ECONOMIC EVALUATION IN KIDNEY TRANSPLANTATION

by
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ABSTRACT

Objective: To identify gaps in the economic literature as it pertains to kidney transplantation in order to inform future research topics as well as to identify the most cost-effective national screening policy for high-infectious risk organ donors and the most cost-effective utilization of marginal quality donated kidneys.

Methods: A scoping review was employed to review the economics and kidney transplantation literature in order to perform a research gaps analysis. A decision tree analysis was used to elucidate the most cost-effective high-infectious risk donor screening strategy and a Markov model was utilized to determine patient phenotypes that would benefit from marginal quality kidney donor organs as well as the cost-effectiveness of accepting certain quality organs for specific patient phenotypes.

Results: The scoping review identified 278 articles from 102 medical and economic journals with research gaps including patient-perspective, pediatrics, and structural/macroeconomic topics. The decision tree analysis found that Selected NAT with ELISA screening strategy was the most cost-effective with an $18,100 savings per QALY compared to the current screening practice (discarding the ELISA Only strategy as a strategy that would not be employed in real practice) . The Markov model identified a large number of patient phenotypes that benefited from high KDPI organ acceptance with increased survival and QALYs and decreased lifetime treatment costs.

Conclusion: Evaluation of the literature related to economics in kidney transplantation afforded the opportunity to address directed research by identifying future research efforts based on formal gaps analysis. The scarcity of organs in transplantation offered a rich opportunity to explore the related economic concepts of individual welfare maximization, allocation efficiency, and cost-effective analysis of competing screening strategies. The results of this dissertation may have policy impacts regarding the funding of associated research and use of marginal quality donated kidneys for transplantation.

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Chronic disease in the U.S. continues to increase in prevalence and constitutes a major fiscal burden. Chronic diseases accounted for seven of the top ten causes of death in 2010[1] and constituted about 78% of health care spending.[2] There has been a concerted national effort to address chronic diseases underlined by the existence of a National Center for Chronic Disease Prevention and Health Promotion.[3] Chief among these chronic diseases are cancers, hypertension and diabetes.[2] Two of the top chronic diseases, diabetes and hypertension, are the leading causes of chronic kidney disease, accounting for up to 67% of cases.[4]

As part of the national effort to combat chronic diseases, and chronic kidney disease in specific, there have been two major steps taken by the U.S. government. First, Congress enacted the Medicare end-stage renal disease entitlement in 1972 designed to more readily help treat chronic kidney disease that progressed to renal failure.[5] Second, Healthy People 2020, the United States government's set of national health goals, has established objectives that deal specifically with combating chronic kidney disease.[6]

End-stage renal disease (ESRD) is one of the natural consequences of chronic kidney disease and is defined by the Centers for Medicare and Medicaid Services as stage V chronic kidney disease (CKD) that requires a regular course of dialysis or a kidney transplantation to improve one's quality of life.[7] A national database, the

United States Renal Data System, records all those with CKD and ESRD and is funded by the National Institute of Diabetes and Digestive and Kidney Diseases which in turn collaborates with the Centers for Medicare & Medicaid Services, UNOS and other ESRD networks to provide up-to-date and accurate information.[8] In 2012, there were 114,813 new cases of ESRD (a 3.7% decrease from 2011) and 636,905 were receiving treatment for ESRD via dialysis or transplantation (a 3.7% increase from 2011).[6]

Overall mortality continues to decrease in ESRD patients with 88,638 ESRD patients passing away during 2012.[6] Morbidity in ESRD includes feeling "unwell" as the body accumulates fluid of which it cannot dispose thereby creating an electrolyte imbalance, the need to spend hours at a dialysis center three times a week, the need to undergo an operation for a transplantation, the need to take immunosuppression medication after transplantation, infectious complications from surgery or from dialysis catheter, and continual need for arteriovenous graft/fistula or central line revisions. A recent meta-analysis of quality-adjusted life years (QALYs) in those with chronic kidney disease reported QALYS of 0.82 (95% CI: 0.74-0.90) for those with renal transplants and 0.69 (95% CI: 0.59-0.80) for those undergoing hemodialysis.[9]

Those with ESRD are entitled to coverage by Medicare and this coverage starts on the first day of the fourth month of dialysis treatments (this waiting period starts even if the individual has not applied to Medicare) unless the individual takes part in a home dialysis training program or has a physician verify that they expect the

individual to be able to finish training and administer their own dialysis treatments in which case the coverage would start in the first month of dialysis.[5] Medicare coverage ends 12 months after the month of dialysis cessation or 36 months after a kidney transplant.[5] Total Medicare claims paid for those with ESRD in 2012 were $28.6 billion, which was 3.5% higher than 2011, and accounted for 5.6% of the Medicare budget while the ESRD population accounts for les than 1% of the total Medicare population.[6]

During 2012, there were 17,330 renal transplants with 5,617 coming from living donors to give a total prevalence of those with renal transplants of 175,978.[6] During the same year, 28,867 ESRD patients were added to the transplant waiting list (both kidney and kidney/pancreas) and the median time on the waitlist was 3.31 years.[6]

Waiting list priorities are based on a point system that includes sensitization (the calculated panel reactive antibody is used to express the expected percentage of donors that will have one or more unacceptable antigens for the candidate), time on the wait list starting when the glomerular filtration rate is less than or equal to 20 mL/min/1.73m^2, age, if the candidate was a prior living donor, human leukocyte antigen (HLA) matching, estimated post transplant survival (based on time on dialysis, diagnosis of diabetes, prior solid organ transplant and age) and blood type.[10]

A Brief History of Transplantation

The first successful kidney transplantation occurred in 1954 between identical twin brothers at the Brigham Hospital in Boston, Massachusetts. It was not until 1960 that a successful kidney transplantation was performed between non-twin siblings.[11] The advent of immunosuppressive medications was a significant moment in transplantation. While the discovery of cyclosporine's ability to suppress the human immune system (and thereby prevent organ rejection in transplantation) was in 1976, it was not until 1983 that the Food and Drug Administration approved its use in transplantation.[11]

The first organ procurement organization (OPO) was organized in 1968 in Boston (the New England Organ Bank).[11] That same year, 1968, the National Conference of Commissioners on Uniform State Laws established the Uniform Donor Card as a legal document in all 50 states through the Uniform Anatomical Gift Act that enabled anybody over the age of 18 to legally donate their organs by legal consent prior to death as well as identify the hierarchy of individuals that could donate another deceased person's organs.[11] In 1973, Congress amended the Social Security Act to provide Medicare coverage to selected individuals with chronic renal disease.[12] Then it was in 1984 that Congress enacted the National Organ Transplant Act (NOTA) which prohibited the trafficking of human organs, established the OPTN (tasked with assuring fair and equitable organ allocation along with setting membership criteria for transplant centers) and established the Scientific Registry

of Transplant Recipients (SRTR, assigned to perform ongoing evaluation of the scientific and clinical outcomes of organ transplantation).[11] Although the OPTN was established in 1984, it was not until 1986 when the first contract to operate the OPTN was awarded by the U.S. Department of Health and Human Services to the United Network for Organ Sharing (UNOS).[11] UNOS is a private, non-profit organization that is tasked with managing the transplant waiting list, matching donors to recipients and maintaining a database of all transplants. In order to help with there task, in 1989 UNOS established 11 regions of the country run by 69 OPO's.[13-15]

Future Research Directions in Transplantation

Transplantation is the treatment associated with the highest survival and quality of life for those with ESRD.[6] In fact, it has been known since at least 1968 that kidney transplantation is the most cost-effective treatment of end-stage renal disease.[17] The question then becomes how to best utilize the scarce resource of donated kidneys in treating ESRD. The importance of this question is underlined by the recent reallocation policies adopted by the OPTN, namely the Share 35 for kidneys in 2005 and Share 35 for livers in 2013. During an era of cost conscious healthcare, economics is an effective research tool in determining both optimum outcomes and cost-effectiveness in the setting of scarce resources. Lionel Robbins, a former head of the economics department at the London School of Economics, gave his famous definition of economics as "the science which studies human behaviour as a relationship between ends and scarce means which have alternative uses" in his

1932 Essay on the Nature and Significance of Economic Science.[18] The advantages of using economics rather than only statistical analysis of allocation efficiency is that economics can evaluate efficiency based on a number of parameters including survival, cost, and utility as they pertain to individuals and societies. This thesis endeavors, in part, to address or improve efficient allocation of donor kidneys in treating ESRD using economic methods and models.

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CHAPTER TWO – MANUSCRIPT #1

Economic Evaluation in Kidney Transplantation: A Scoping Review and Gaps Analysis[1]

Abstract

Objectives: To systematically review the literature related to the economic evaluation of kidney transplantation in order to determine the extent of current research and identify gaps for future research.

Data Sources: We searched 4 medical and 1 economic electronic databases. All searches were from the earliest dates available through September 13, 2014. Additional articles were identified via hand-searching reference lists of review articles and other pertinent articles.

Study Selection and Data Extraction: Articles were included that dealt with an economic evaluation of human kidney transplantation. Exclusion criteria included articles that did not include original work (i.e. reviews), were not in English and were not journal articles or economic working papers (e.g. commentaries, theses,

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abstracts). Full text data abstraction included qualitative and quantitative parameters with the intent to perform a gaps analysis for future research.

Data Synthesis: A total of 278 articles were included and they spanned a 46-year period from 1968-2014 with over 70% published after 1999. The most common topics included immunosuppression drugs, infectious disease prophylaxis, dialysis versus kidney transplantation, organ allocation and the potential market for donor organs. The majority of articles were from the United States and they originated from 68 medical journals and 34 economic journals or working paper centers. There were 51 articles dealing with costing, 149 utilizing cost-effectiveness, 65 employing economic modeling, 3 performing systematic reviews with meta-analyses and 10 exploring the qualitative financial environment of individuals and the economy. Research gaps were identified in every parameter used to evaluate the studies and a new system of gaps analysis for scoping reviews was also proposed.

Conclusions: The field of economic evaluation in kidney transplantation is still in a relatively early stage. The research gaps identified through this study provide multiple areas of fertile ground for economist and medical practitioner collaboration.

Introduction

End-stage renal disease (ESRD) is defined as renal failure requiring dialysis or transplantation for patient survival or an estimated glomerular filtration rate less than 15 mL/min/1.73m^2 [1]and it affects over 590,000 individuals in the United States with over 116,000 new ESRD patients each year.[2] ESRD carries a mortality similar to that of an early/mid-stage lung cancer at five years[3,4] and the main contributors to the continuously rising rate of ESRD are diabetes (44%) and hypertension (28%).[2] Each year, over $47 billion is spent on ESRD care with Medicare spending about $87,000 per year per patient on hemodialysis and about $33,000 per patient per year after a kidney transplantation.[2] Kidney transplantation provides improved survival, better quality of life and lower cost of care compared to dialysis in ESRD patients[5,6] and the main problem facing the transplantation community is the lack of available donor organs. From 2009 to 2010, adult kidney transplants only increased by 0.8% to a total of 16,843 while the waitlist increased by 6% to 86,620.[2] As kidney transplantation is the most cost-effective way to alleviate the mortality and morbidity of ESRD, the question becomes how to use the scarce resources of donated kidneys most effectively and efficiently within the budget constraints of Medicare and society.

Economic evaluation addresses the restrained optimization of resources premise and has been used in the literature to address issues including elephant poaching,[7] traffic congestion,[8] epilepsy surgery,[9] and lung cancer management in the era of personalized medicine.[10] Economic evaluation also has been used in the kidney

transplantation literature to assess new technologies, donor initiatives, markets for organs and the use of expanded criteria donor kidneys, to name a few instances. These studies vary widely in topic, economic evaluation technique, cohorts and study parameters.

The evaluation of an entire field of literature with the identification of research gaps in order to prioritize future research is an increasingly important endeavor meant to assure future research efforts are optimized instead of carried out in the traditional *ad hoc* approach.[11-13] Traditionally, journal articles have pointed out areas of future research based on concurrently discovered research gaps in the Discussion sections as closing thoughts. It is now recognized that research gaps analysis should be carried out before embarking on any particular research in order to assure the proposed research topic and technique are well informed to make the most advantageous use of research resources and efforts. Several scientific and government organizations have dedicated research or are pursuing methodologies in this very area of gaps analysis and they include The Patient Centered Outcomes Research Institute (PCORI),[14] the Institute of Medicine,[14] Cochrane,[15] and the U.S. Food and Drug Administration.[16] A new and increasingly popular method intended to facilitate gaps analysis is the scoping review.[11-13]

The objective of this paper is to detail future research opportunities in the field of economic evaluation in kidney transplantation through a scoping review and a methodologically driven gaps analysis. We believe this will be helpful as, to our

knowledge, there is no study that summarizes the sum total of economic literature written on kidney transplantation nor identifies current research gaps in the literature from such a study.

Methods

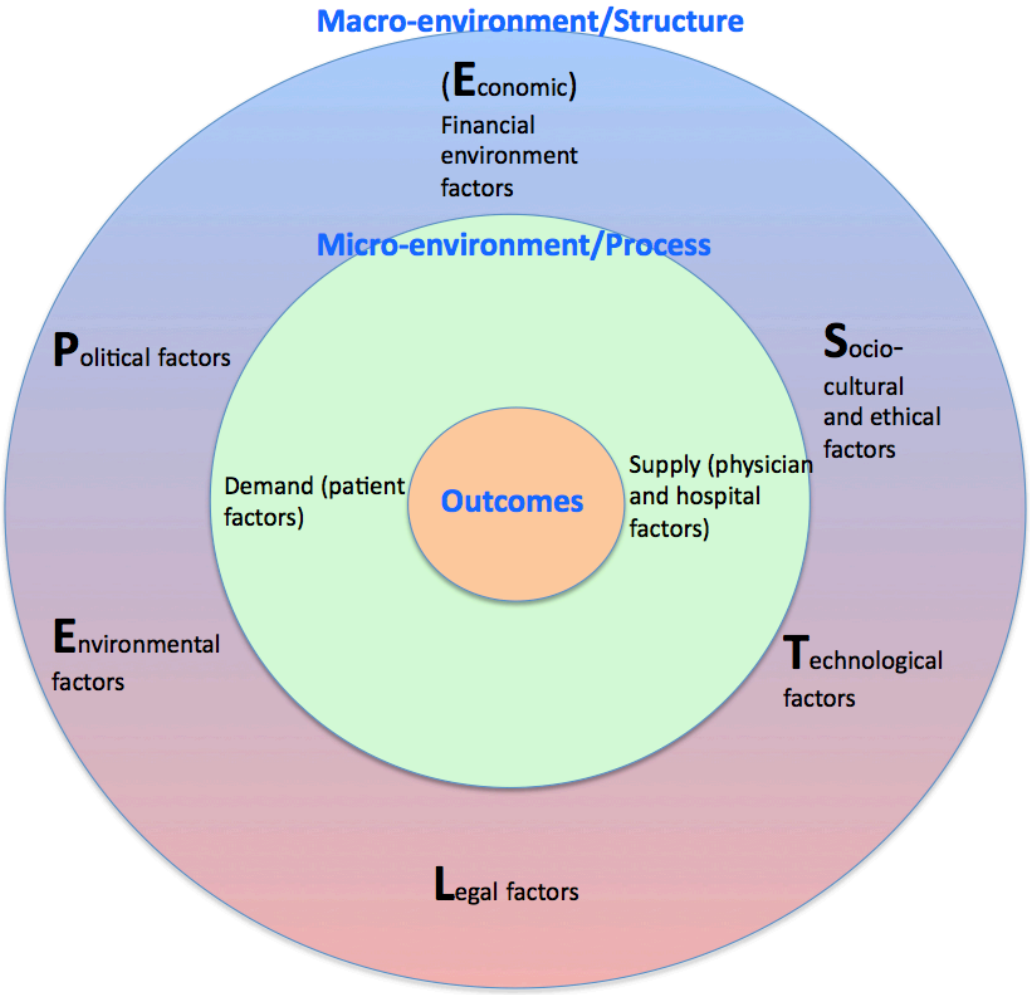
Four medical electronic databases (PubMed/MEDLINE[17], SciVerse Scopus[18], Elsevier Embase[19], and the Cochrane Library[20]) and two economic electronic databases (EBSCO EconLit with Full Text[21] and the Center for the Evaluation of Value and Risk in Health Cost-Effectiveness Analysis Registry[22]) were searched over their entire coverage dates for relevant articles in the English language. All searches were performed to and including September 13, 2014. Two librarians trained in systematic reviews assisted in creating and reviewing the search strategies (Appendix 1). Reference lists of review articles and other relevant articles were hand-searched to identify additional articles.

All articles that included an economic evaluation of human kidney transplantation were included. Articles were excluded if they did not provide original work (i.e. reviews), were not in English or were not journal articles or economic working papers (e.g. commentaries, theses, abstracts). Economic evaluation was defined as dealing with costing, cost-effectiveness, financial strategies or economic theories and models.

Two authors (TE and IH) reviewed all article titles and abstracts and retained only those articles deemed eligible according to the inclusion and exclusion criteria stated above. All articles were retained where at least one author deemed the article eligible. The resultant articles were then subject to full article review for final eligibility into the study. A single author (TE) performed the full text review that resulted in the final number of articles for study analysis.

Articles were categorized in two manners: by topic and by evaluation technique. Topic categorization was aided by the development of a conceptual framework. In order to account for the breadth and depth of literature sought in this study, a conceptual framework was designed from the viewpoint of economic evaluation of macro- and micro-environmental elements as they relate to kidney transplantation outcomes (Figure 1).

Figure 1. Conceptual Framework for Article Categorization.



Overall, the Donabedian medical care quality evaluation model of structure, process and outcome was employed where the structure component mirrors macroeconomic concepts and the process component parallels microeconomic concepts.[23] The *structure* portion of the conceptual model, defined as the environment over which the transplant candidate or provider have no direct control,

was further characterized according to a PESTLE analysis.[24] PESTLE analysis is commonly used in business practice to evaluate how best to position a business within its macro-environment in terms of industry areas of growth and potential future operations. The PESTLE categories were adapted for the purposes of this study and the categories were defined as: 1) Political: society's coverage of kidney transplantation, 2) Economic/financial environment: qualitative financial burden on nation and individuals, 3) Socio-cultural and ethical: society's view and willingness to participate in kidney transplantation or to allow a market for organs, 4) Technological: newly introduced diagnostic or treatment options including screening protocols, donor kidney preservation techniques and new immunosuppression or induction regimens, 5) Legal: national donor organ allocation practices, and 6) Environmental: the environment of treatment options a transplant candidate finds including dialysis and the availability, quality and outcomes of donor organs.

The *process* portion of the conceptual model deals with the interaction between the transplant candidate (demand side) and their physician or hospital provider (supply side) in terms of the associated factors over which they have direct control. The *outcomes* portion of the model is placed at the center of the *structure* and *process* macro- and micro-environment.

Each paper was also then categorized according to the evaluation technique employed which included costing, cost-effectiveness, economic modeling or theories and qualitative financial impact.

Research Gaps Analysis

With the intent to describe research gaps, the guidelines for the analysis of systematic reviews according the Agency for Healthcare Research and Quality (AHRQ)[25] were employed since no research gaps methodology exists for scoping reviews like this one. Along with the AHRQ suggested "PICOS" data abstraction of study population, intervention, comparison group, outcomes, setting as well as reason for any gap, additional data including topic categorization, evaluation technique, year, title, author, journal, country, study time interval, study perspective, use of Markov models, whether the year of currency was specified and whether any of the authors were from industry (one rough marker for potential conflict of interest bias) were recorded. Qualitative and quantitative data abstraction was performed by one author (TE).

The AHRQ uses an A-D system for characterizing potential research gaps in systematic reviews. In this manner, all the qualitative data can be consolidated into four basic gaps categories. In adapting these AHRQ guidelines to this scoping review, the four characterizations of gaps were defined as 1) A: insufficient or imprecise data taken to mean no significant conclusion, 2) B: biased information taken to mean single-center studies with no statistically significant result or

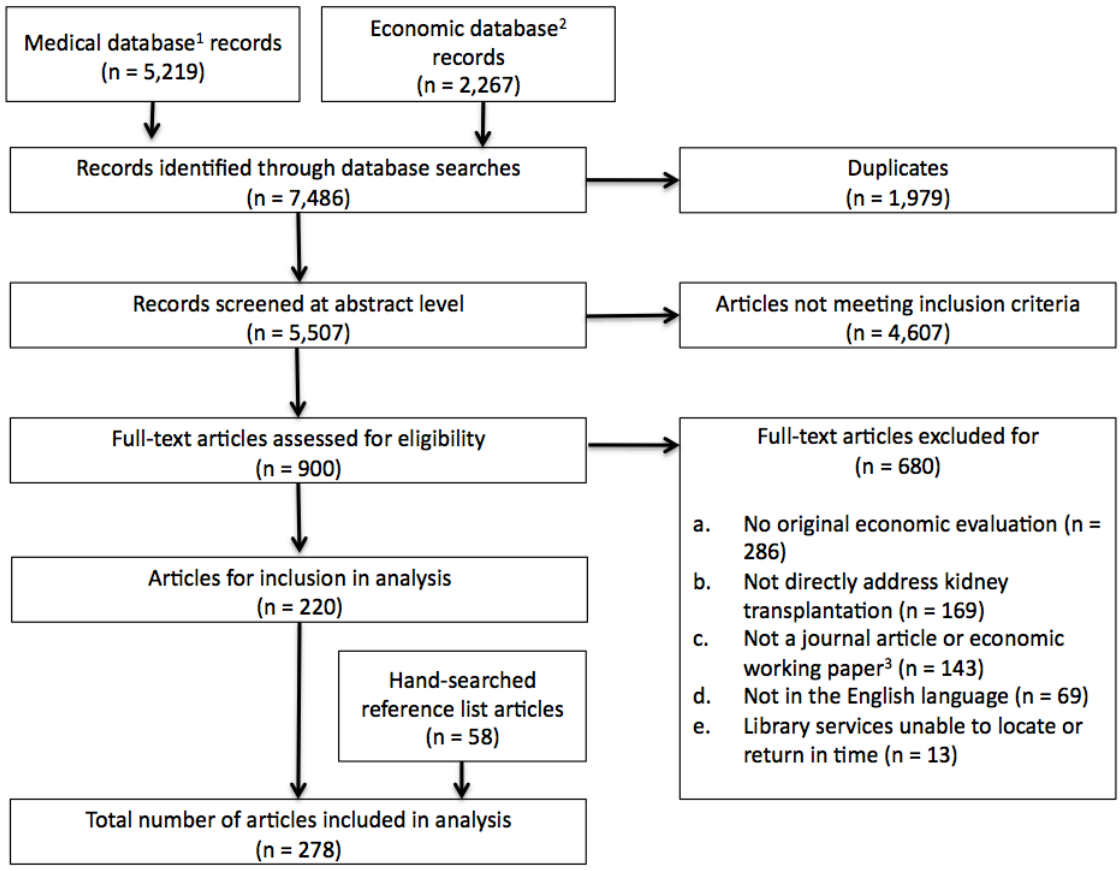
sensitivity analyses, 3) C: inconsistent or unknown consistency of results taken to mean any topic that only had one study or any group of five or less studies that had conflicting conclusions, and 4) D: not the right information taken to mean study results with a time horizon less than 5 years (knowing that kidney donor organ survival is still 83% at 5 years and 58% at 10 years).[3]

Results

Total Number of Articles by Year, Topic, Country and Journal

The electronic search resulted in a total of 5,507 articles with no duplicates (Figure 2).

Figure 2. Article Search Flow Diagram



[1]Medical databases included MEDLINE, Scopus, Embase and the Cochrane Library

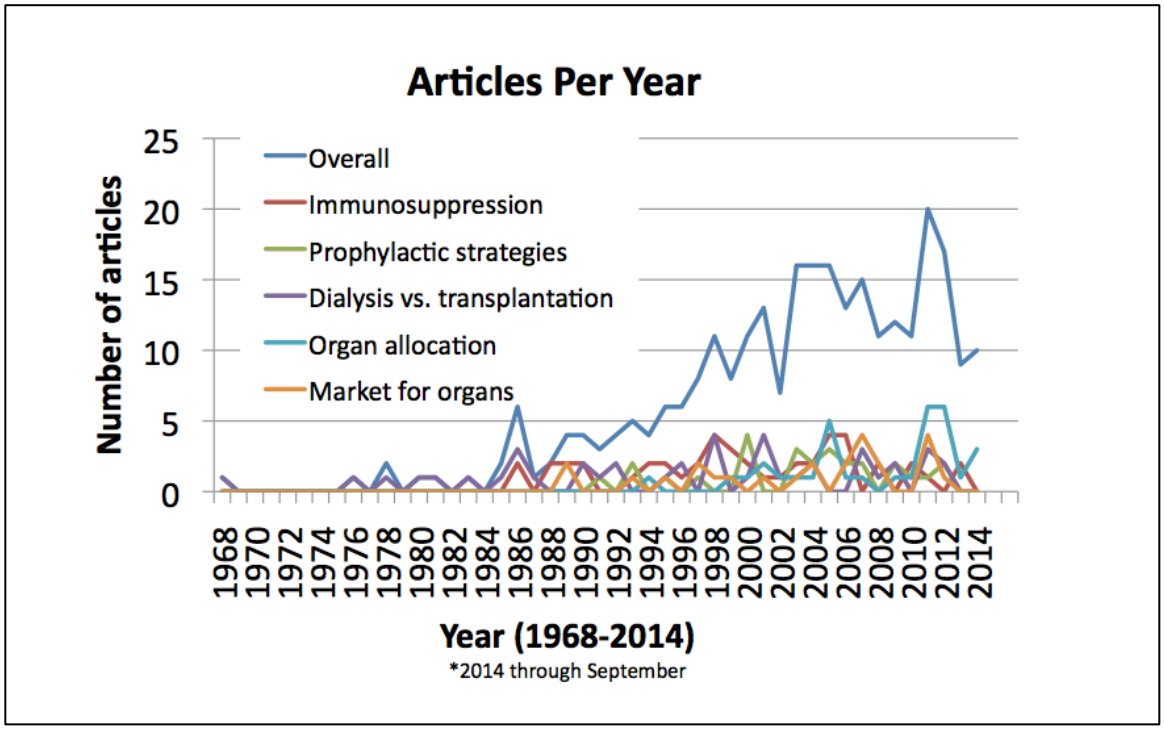
[2]Economic databases included EconLit with Full Text and the Cost-Effectiveness Analysis Registry of Tufts University

[3]These other sources include commentaries, editorials, personal viewpoints, personal perspectives, book reviews, books, newspapers, interviews, theses, dissertations, abstracts, poster presentations, symposia and workshops

Review of titles and abstracts resulted in 900 articles for full review. Full text review produced the final list of 278 eligible articles (Appendix 2) that spanned 46 years, 1968-2014, with 11 years where no articles were identified (1969-1975,

1977, 1979, 1982, 1984). Seventy-one percent of the articles were published in 2000 or later (Figure 3) with the increase in articles being largely driven by the evaluation of new medicines and technology as applied to transplantation.

Figure 3. Graph of the Number of Overall and Four Most Common Articles Written per Year, 1968-2014 (* through end of September 2014)



The most common topics involved immunosuppressants, infectious disease prophylaxis, dialysis versus kidney transplantation, donor organ allocation and a potential market for donor organs (Table 1).

Table 1. Articles Categorized within Conceptual Framework

Conceptual framework heading	Number of articles in category
TECHNOLOGICAL	**96 (35%)**
a. Immunosuppression medications	46
b. Prophylaxis	27
c. Induction therapy	18
d. Laparoscopic donor nephrectomy	5
ENVIRONMENTAL	**53 (19%)**
e. Dialysis versus transplantation	43
f. Organ quality	10
LEGAL	**31 (11%)**
g. Allocation	31
SOCIO-CULTURAL and ETHICAL	**25 (9%)**
h. Market for organs	25
POLITICAL	**22 (8%)**
i. Coverage	22
PROVIDER-LEVEL FACTORS	**18 (6%)**
j. Hospital/physician factors	14
k. Evaluation process	3
l. Accept/reject decision	1
PATIENT LEVEL FACTORS	**18 (6%)**
m. Living donors	7
n. Adherence	5
o. Quality of life measurements	2
p. Financial strain	2
q. Accept/reject decision	2
Economic/Financial	**15 (5%)**
r. Economic considerations	15

Even these most popular topics only averaged between 0.7-1.3 articles per year over the 35 years where articles were identified. The remaining topics each contributed 18 articles or less over the 46 year time span. One hundred forty-six of the articles (53%) were from the United States with the next highest counts coming from Canada (9%), the United Kingdom (6%), and Australia (4%) (Table 2).

Table 2. Country of Senior Author

Country	Total number of articles per country
United States	146
Canada	24
United Kingdom	17
Australia	10
The Netherlands, Spain	9
France	7
Switzerland	6
Germany	5
Chile, Iran, Italy, Japan, Taiwan	4
India, Sweden, Turkey	3
Hungary	2
Austria, Belgium, Bosnia & Herzegovina, Brazil, Bulgaria, Dominican Republic, Greece, Israel, New Zealand, Norway, Poland, Saudi Arabia, Serbia, South Africa	1

No other country contributed more than 9 articles in this analysis (noting again that only articles written in English were included). All of the articles came from 102 journals (68 medical journals and 34 economic journals or working paper centers) and 82% of the articles were found in medical journals.

Only three medical journals contained 5% or more of the total articles (Transplantation Proceedings 16%, Transplantation 10% and the American Journal of Transplantation 5%) while only six economic sources contained 1% or more of the total articles (The American Economic Review 1%, Contemporary Economic Policy 1%, National Bureau of Economic Research Working Papers 1%, Economic

Inquiry 1%, Journal of Economic Perspectives 1% and Journal of Economic Theory 1%).

Qualitative Evaluation of Studies with Identification of Gaps

Population

The intervention and comparison populations were evaluated based on age and study size. The majority of articles, 63%, did not explicitly state whether the population was adult or pediatric or both. Thirty-one percent of the articles stipulated adult populations while only 0.4% examined exclusively pediatric populations and 6% stated that the population was a mixed adult and pediatric population. Study size ranged from 1-274,832 with 29% of papers relying on single center populations and 18% relying on multi-center populations. Of note, 20% of the costing and cost-effectiveness papers used Markov modeling of populations (Table 3). Gaps exist in pediatric research and large-population, multi-center studies.

Table 3. Study Characteristics by Study Type

Characteristic	Costing	Cost-effectiveness	Economic Theory	Systematic Review and Meta-analysis	Financial impact	Totals (percentages)
Cohort type						
Prospective	6	26	7	0	0	14%
Retrospective	45	123	58	3	10	86%
***Perspective**						
Payer/Medicare/hospital/national health insurance/society	47	148	56	1	3	92%
Patient	6	7	13	2	8	13%
Age of population						
Adults	20	54	7	0	5	31%
Pediatrics	0	1	0	0	0	0.4%
Both adults and pediatrics	5	8	1	0	2	6%
Not specified	26	86	57	3	3	63%
****Study size**						
Single center [population range]	21 [1-524]	52 [7-1023]	5 [86-391]	0	3 [77-129]	29%
Multi-center [population range]	4 [52-3,181]	38 [30-68,657]	6 [384]	0	3 [254-305]	18%
Markov model (only including costing and CEA papers)	1	38	N/A	N/A	N/A	20%
One or more authors from pharmaceutical company (only including costing and CEA papers)	5	21	0	0	0	9%
Year of currency specified	29	97	N/A	N/A	N/A	63%
***Time horizon of study (only including costing, CEA and financial impact papers)**						
≤ 1 year	22	61	N/A	N/A	0	39%
1-5 years	20	33	N/A	N/A	2	26%
>5-10 years	4	19	N/A	N/A	1	11%
> 10years	3	37	N/A	N/A	1	19%
Unknown	2	0	N/A	N/A	5	3%
****Gaps analysis**						
A	5	2	0	0	2	3%
B	22	32	5	0	5	23%
C	17	12	5	0	5	13%
*****D	42	79	1	0	2	44%

Table 3 notes: * A number of studies provided more than one perspective; ** When documenting "Study size," single center, multi-center and national database studies were documented when specifically mentioned in the article; *** Time horizon is how the results were reported, not necessarily the time horizon of the model input data if used; **** A: insufficient data to produce significant results, B: biased data use, C: unknown consistency of results due to rarity of topic, D: insufficient time interval; ***** Timeline of results was not applicable in 65 of the studies so the denominator in this case was 213 instead of 278

Intervention and Comparison Groups

Since scoping reviews cover such a broad range of experimental interventions, the intervention and comparison groups were exclusively described by topic categorization (Table 1). Gaps exist in financial/economic environment, physician/provider and patient factors.

Outcomes and Timing/Time Horizon

Again, since scoping reviews deal with a very large variety of interventions, outcomes were described based on evaluation technique, whether they specified the currency year, whether one of the authors was from industry, and the time horizon of the study results. The most common evaluation technique was cost-effectiveness with 149 articles, followed by economic theory/modeling with 65 articles, costing with 51 articles, qualitative financial impact with 10 articles and systematic reviews with meta-analyses with 3 articles. Only 63% of the costing and cost-effectiveness articles specified a currency year and almost 40% of the same articles used a time horizon of one year or less. Another 26% used a timeline of 1-5 years making it a full two-thirds of articles that dealt with time horizons of 5 years or less. Less than 10% of papers had an author from industry (Table 3). Gaps exist in economic

modeling, meta-analyses, time horizons over 5 years, and stating currency year consistently.

Of note, costing evaluations did not have an "effect" aspect and these types of articles included, for example, the cost to Medicare of acute rejection,[26] the cost to hospitals of invasive fungal infections,[27] the difference in costs between high- and low-volume centers,[28] and the cost to the hospital of a living donor nephrectomy.[29] Cost-effective evaluations reported results with both a cost and effect component and included cost-utility evaluations.

Economic modeling topics included supply and demand, welfare maximization, combination optimization, economies of scope, monopsonies, and game theory. The three systematic review and meta-analysis articles evaluated quality of life differences between dialysis and transplantation patients[30,31] and the cost differences between dialysis and transplantation.[32] There were ten qualitative economic/financial impact articles that were distinguished from costing or cost-effectiveness articles for their non-monetary/qualitative results of financial or economic events. For example, one study was a descriptive survey of all kidney transplant centers in the US to assess the association between patient non-adherence as related to personal financial strain (in a qualitative, not quantitative, sense) that their patients faced[33] and another was the association between the "economic environment" (as determined by the Dow Jones Industrial Average,

unemployment and the Consumer Price Index) and kidney transplantation outcomes.[34]

Setting

Setting was described by cohort type and study perspective. The majority of studies, 86%, were retrospective and the vast majority, 92%, did not include the patient perspective (Table 3). Gaps exist in prospective studies and studies taking the patient perspective.

Gaps analysis was also performed by a synthesis of the qualitative evaluation data of the articles into categories A-D as described in the Methods section. The most common gap was insufficient time interval ("D") which was present in 44% of the articles, followed by biased information ("B") which was present in 23% of the articles, inconsistent results or unknown consistency ("C") which was present in 13% of the articles and insufficient or imprecise data ("A") which was present in 3% of the articles (Table 3).

Discussion

Scoping reviews, or scoping studies, are a relatively new approach to summarizing literature with the first methodological framework advanced in 2005.[35] Since then, there have been a number of scoping reviews including topics in complementary and alternative medicine, health system report cards, arts-based health research and nursing.[36-39] Scoping reviews are usually carried out for the purposes of

evaluating the breadth of research on a topic, determining if a full systematic review should be pursued, summarizing research findings or for identifying gaps in the literature.[35] Regardless of its ultimate goal, published scoping review papers have the ability to reduce duplication of literature reviews and guide subsequent research.[11] We believe this study to be the first scoping review in the economic evaluation of kidney transplantation.

As there is no generally accepted method to perform gaps analyses in scoping reviews, we adapted the AHRQ guidelines for research gaps for systematic reviews to this study in order to bring a level of study quality evaluation to this scoping review which is normally not present in scoping reviews.[13,35] However, the adaptation needed to broaden the summary gaps categories of A-D for the scoping review made it so the A-D categories were just one more way to evaluate the studies instead of serving as an all-inclusive gaps summary.

Through our study, we found that gaps analysis for systemic reviews was inadequate for scoping reviews and we propose that scoping review gaps analysis follow an individualized PICO(T)S ("T" for timing) analyses. Population gaps can be assessed on age, study size and whether the population was mathematically generated. Intervention and comparison group gaps can be assessed by conceptual model topic using our Donebedian/PESTLE model. Outcome gaps can be assessed by technique categorization, results presentation (e.g. statement of currency year, identification of potential industry biases), insignificant conclusions (the "A" gap in

this paper), biased information from a single center (the "B" gap in this paper) and assessment of rarity or conflicting results of similar studies (the "C" gap in this paper). Finally, setting and timing gaps can be assessed by cohort type, study perspective, and whether there was an insufficient time horizon (the "D" gap in this paper).

As scoping reviews can deal with such a wide range of topics, the addition, elimination or modification/individualization of some of the parameters will likely be needed, but the general framework and parameters presented here should serve across most, if not all, topics. Also, we believe that there is no "gap summary" that incorporates all the information in the gaps analysis but that each element in the PICO(T)S evaluation needs to be appreciated individually to guide future research. As it is likely that no future research project will incorporate all research gaps identified, it makes sense that each gap in the PICO(T)S evaluation be individually identified instead of trying to bundle them all into one or a few "overall summary gaps."

Aside from a proposed gaps analysis framework for scoping reviews, we feel that another contribution of this paper is the construction of a conceptual framework designed to account for the breadth and depth of literature. While the Donabedian model[23] gave the model a general structure, we used the PESTLE evaluation methodology[24] to provide a more in-depth and sophisticated categorization of the material. Aside from data presented in the Results section, there are three further

items to note about the conceptual model. First, it could be argued that improvements or advances in "Macro-economic" topics could potentially have more impact than those in the "Micro-economics" topics since "Macro-economics" topics can increase the volume of transplants while "Micro-economics" topics lead to more efficient and effective use of resources for those already involved in transplantation.

Second, the amount of research activity in a certain topic can direct future researchers in one of two directions. Topics of high research traffic may represent areas of current interest (encouraging further research) or areas that have already been adequately treated (potential disincentive for future research). Topics of low research traffic may represent areas were there is no current data or no political will (potential disincentive for future research) or areas where there is an opportunity for exploration (encouraging for further research). Third, the conceptual framework may facilitate the visual connection between different areas of research. For example, by looking at the model, it is easy to consider how the advantages of markets for organs in the Socio-cultural and Ethical Factors section interact with the other elements of the "Macro-economic" section, namely Political and Legal Factors, which may then need further research or advocacy in terms of market for organs.

Beside the summary of the literature and gaps identification in the Results section, there are a number of other items of interest garnered from this scoping review. First, in terms of volume, the literature in this area is relatively small with only 278

articles identified over 46 years so this is a relatively young field with great room for expansion. For comparison, a 2004 paper on keeping up with the medical literature for primary care medicine estimated that 7,287 articles were published monthly just in that field.[40]

Second, it is notable that "Macro-economic" topics that have such a large opportunity to benefit many people have not attracted more attention. For example, research in the economic benefit of using high-infectious risk organs (an Environmental factor) or of future markets in donor organs (a Socio-cultural and ethical Factor) can lead to more research in how Political or Legal Factors could be influenced to possibly accept these economically beneficial activities.

Third, with the passing of the Patient Protection and Affordable Care Act in 2010 leading to the establishment of the Patient-Centered Outcomes Research Institute (PCORI), there will likely be much more emphasis on patient-related outcomes and preferences. This is significant since only 13% of the identified articles took a patient perspective meaning that this is plenty of room for research in patient-centered outcomes in kidney transplantation.

Fourth, almost half of the articles did not specify the currency standard year. This belies the need for more of a standardization of the literature in terms of evaluation techniques and manner of reporting results. In fact, the literature is dispersed over 102 journals with only three journals having over 5% of all articles found in the last

46 years. There may be a benefit of condensing the literature to a much smaller number of journals which in turn might foster more specialization and appropriate guidelines.

There are several limitations of this paper. First, the electronic database searches were not likely to find very early papers on economics and transplantation. There were 11 years where no articles were found and all of the missing years were before 1985. However, over 70% of the articles in this study were published in 2000 or later so any articles missed before 1985 may be more of historical significance rather than analytic significance. Second, and related to the first limitation, is the fact that 58 of the 278 articles (21%) were found by hand searching pertinent reference lists rather than through the electronic search. However, two librarians trained in systematic reviews deemed the searches appropriate and our search was wide, resulting in 7,486 hits. It is likely that the tagging of topics in electronic databases has changed over the years and that many were not tagged sufficiently to show up in our search. Third, the iterative process, as described in the Arksey and O'Malley[35] and Levac et al.,[13] was handled with two authors reviewing titles and abstracts for review, but only by one author for full article review and data abstraction. However, the broad scope of scoping reviews requires a practical assessment of resources and time and we felt comfortable with a single author full text review and abstraction as that single author had training in both economic evaluation and medicine. Fourth, we used guidelines for systematic reviews for gaps

analysis and while these guidelines were not optimal for scoping reviews, we used them as a basis to provide suggested guidelines.

In conclusion, there are a number of reasons why contributing to the economic literature in kidney transplantation is exciting and attractive. First, the field is still in the early stages although there has been a large increase in activity in recent years. Second, there is a great opportunity to affect many end-stage renal disease patients in need of transplantation who carry a large clinical and financial burden. Third, there are a large variety of topics and techniques that are available to explore in this field. In addition, there are several large and comprehensive databases (United Network of Organ Sharing, Scientific Registry of Transplant Recipients, and United States Renal Data System) as well as the opportunity to perform quasi-experimental research due to the fact that transplantation care varies by surgeon, hospital, and organ procurement organization region. In summary, studying kidney transplantation through the lens of economic evaluation has the opportunity to have a large impact in patient care and there are a wide variety of topics and techniques available for clinicians and economists to team together to address.

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Appendix 1. Boolean Search Strategies

1. PubMed/MEDLINE

"Economics" [TIAB] OR "economic" [TIAB] OR "utility theory" [TIAB] OR "utility theories" [TIAB] OR "macroeconomic factors" [TIAB] OR "microeconomic factors" [TIAB] OR "factors, microeconomic" [TIAB] OR "compensation and redress" [TIAB] OR "cost and cost analysis" [TIAB] OR "capitalism" [TIAB] OR "resource allocation" [TIAB] OR "health care rationing" [TIAB] OR "fees and charges" [TIAB] OR "health planning support" [TIAB] OR "insurance" [TIAB] OR "single-payer system" [TIAB] OR "medical savings accounts" [TIAB] OR "health care sector" [TIAB] OR "medical indigency" [TIAB]

AND

"Transplants" [TIAB] OR "organ transplantation" [TIAB] OR "transplant" [TIAB] OR "transplantation"[TIAB] OR "grafts" [TIAB] OR "graft" [TIAB] OR "tissue transplants"[TIAB] OR "tissue transplant" [TIAB] OR "organ transplants" [TIAB] OR "organ transplant" [TIAB] OR "organ grafts" [TIAB] OR "organ graft" [TIAB] OR "tissue grafts" [TIAB] OR "tissue graft" [TIAB] OR "tissue transplantation" [TIAB]

NOT

("animals"[MeSH Terms] NOT ("humans"[MeSH Terms] AND "animals"[MeSH Terms])

* [TIAB] = search of title and abstract

2. Embase

'economics':ab,ti OR 'economic':ab,ti

AND

'transplants':ab,ti OR 'transplant':ab,ti OR 'transplantation':ab,ti

NOT

'animals':ab,ti OR 'heart transplant':ab,ti OR 'heart transplantation':ab,ti OR 'lung transplant':ab,ti OR 'lung transplantation':ab,ti OR 'pancreas transplant':ab,ti OR 'pancreas transplantation':ab,ti OR 'face transplant':ab,ti OR 'face transplantation':ab,ti

* ab,ti = search of abstracts and titles

** further search modification included limiting the search by un-checking the radio button for MEDLINE, un-checking the radio button for 'include sub-terms/derivatives' and checking the radio button for 'major focus in paper'

3. Scopus

TITLE({Economics} OR {economic})

ABS({Economics} OR {economic})

AND

TITLE({Transplants} OR {transplant} OR {transplantation})

ABS({Transplants} OR {transplant} OR {transplantation})

NOT

TITLE({animals} OR {heart transplant} OR {heart transplantation} OR {lung transplant} OR {lung transplantation} OR {pancreas transplant} OR {pancreas transplantation} OR {face transplant} OR {face transplantation})
ABS({animals} OR {heart transplant} OR {heart transplantation} OR {lung transplant} OR {lung transplantation} OR {pancreas transplant} OR {pancreas transplantation} OR {face transplant} OR {face transplantation})

* final search in order to cover both title and abstracts:

(((TITLE(**{Economics}** OR **{economic}**)) AND (TITLE(**{Transplants}** OR **{transplant}** OR **{transplantation}**))) AND NOT (TITLE(**{animals}** OR **{heart transplant}** OR **{heart transplantation}** OR **{lung transplant}** OR **{lung transplantation}** OR **{pancreas transplant}** OR **{pancreas transplantation}** OR **{face transplant}** OR **{face transplantation}**))) OR (((ABS(**{Transplants}** OR **{transplant}** OR **{transplantation}**)) AND (ABS(**{Economics}** OR **{economic}**))) AND NOT (ABS(**{animals}** OR **{heart transplant}** OR **{heart transplantation}** OR **{lung transplant}** OR **{lung transplantation}** OR **{pancreas transplant}** OR **{pancreas transplantation}** OR **{face transplant}** OR **{face transplantation}**)))

4. Cochrane Library Database

"Transplant," "transplants," or "transplantation"; all searched separately

* the search was limited to titles, abstracts, keywords, economic evaluations and reviews

5. EconLit with Full Text

"Transplant" OR "transplants" OR "transplantation"

* the search included full texts of the articles as well as any related words

6. The Cost-Effectiveness Analysis Registry (Tufts University)

"Transplant," "transplants," "transplantation"

* the basic search function was used so each of the three topics was searched separately

Appendix 2. Bibliography of Scoping Review Articles

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CHAPTER THREE – MANUSCRIPT #2

Cost-Effectiveness of Five Infectious Disease Screening Strategies in Deceased Donor Kidneys[2]

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Abstract

Introduction: Due to a growing disparity between the number of wait listed transplant candidates and available organs for transplant, here has been interest in the utilization of donated kidneys at high risk for infectious disease transmission as a means to increase the donor kidney pool.

Objectives: To assess the cost-effectiveness of five national screening policies for high infectious risk kidneys in order to properly identify uninfected organs and increase their use.

Methods: A decision-tree analysis was conducted comparing five strategies of screening organ donors for HIV and HCV: the current national practice (a mixture of ELISA Only, Selective NAT with ELISA, and Universal NAT with ELISA), ELISA Only, Selective NAT with ELISA, Universal NAT with ELISA and NAT Only. Probabilities, costs and QALYs were taken from the literature. All costs were reported in 2015 US dollars and the perspective was that of the payer/Medicare.

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Results: Outside of the ELISA Only strategy, Selective NAT with ELISA was the most cost-effective screening strategy and was associated with the most number of uninfected organs transplanted, the least number of uninfected organs discarded, the most number of QALYs, the least number of discarded QALYs and the least overall cost but all at the cost of transplanting 3 more infected organs per year over the current national screening practice. Compared to the current national screening practice, Selective NAT with ELISA saves $18,100 per QALY gained and carries a screening budget impact to Medicare of $1,088,336 saved per year.

Conclusions: The Selective NAT with ELISA screening strategy is the most viable, cost-effective national screening policy for high infectious risk donor organs. National guidelines should be determined in how selective NAT should be applied to avoid increased costs, lost organs and subsequently lost QALYs.

Introduction

There were 111 fewer adult kidney transplants in 2011 compared to the previous year while the kidney transplant list grew 4% in that same timeframe.[1] Time on the waitlist is associated with increased mortality[2-8], decreased quality of life[9] and disproportionately high Medicare charges.[10] There have been many efforts to

increase the pool of organs including encouraging more living and deceased donations, expanding the criteria of organs that are used, exploring a market for donated organs and funding basic research in stem cells and xenotransplantation.[11-15] Another specific area of interest is in the appropriate utilization of donated organs at high risk for infectious disease transmission.

Centers for Disease Control and Prevention (CDC) high-risk donors (HRD) are those at higher risk for human immunodeficiency virus (HIV) and hepatitis C virus (HCV) infection than the general population even in the face of negative serologic testing.[16] This higher risk is conferred through nine behaviors or being on hemodialysis, as defined by the U.S. Public Health Service, since blood testing may still be negative due to the possibility of window period (WP) infections.[17-20] The CDC states that these organs should not be used except in emergent or life-threatening instances where the benefits outweigh the risks.[19] There have been at least seven reported incidents of viral disease transmission from a solid organ donor to transplant recipients.[21-23] The publicity surrounding the transmission of infectious disease through solid organ transplantation lead to at least a third of transplant surgeons to change their practice in decreasing their use of HRDs.[22,24,25] One option to decrease the transmission of infectious diseases would be to use nucleic acid testing (NAT) in screening donor organs as it is a more sensitive test than the currently UNOS mandated enzyme-linked immunosorbent assay (ELISA).

The reason for interest in HRDs is that they constitute approximately 9% of donors where at least one organ is recovered[26] and their actual risk of infection is relatively low (ranging from 0.09-12.1 per 10,000 donors based on the serologic window period for HIV and from 0.26-300.6 infections per 10,000 donors based on the serologic window period for HCV).[16,24,27] The volume of uninfected HRDs that are discarded each year due to their HRD status, if used, would increase the number of uninfected organs available for transplant each year and it could be done with higher overall survival and QALYs with decreased transmission of diseases (one study has shown that hepatitis C transmission on hemodialysis can occur more frequently than if all HRD organs were transplanted) and overall cost.[24,28] In addition, outcomes of HRD transplants, in terms of patient and graft survival, are no different when compared to standard criteria donor organs and models show their benefits outweigh their risks.[28-30]

The main advantage of using NAT in order to better identify uninfected HRDs would be in the increased willingness of transplant surgeons to use NAT negative HRDs since NAT would likely only prevent a small number of potential serologic window period infections.[25] The use of NAT in organ transplantation has not been mandated as of yet[20] mostly due to concerns of the false positive rate (leading to an increase in the discarding of non-infected organs), cost, availability and length of time needed to receive the results.[25,31-33] This has left relative equipoise in the use of NAT with only 40-50% of organ procurement organizations (OPOs) always performing NAT,

20-30% of OPOs never performing NAT and the remaining OPOs selectively performing NAT.[33,34]

The objective of this study was to determine the cost-effectiveness of five different national donor organ screening strategies, with and without the use of NAT, in providing the most number of uninfected kidney transplants, the least number of infected kidney transplants and the least number of discarded uninfected organs at an acceptable cost-effective ratio of cost per QALY. The significance of establishing the most efficient use of NAT testing would be to increase the deceased donor pool and decrease those on the waiting list with the concomitant increase in transplant candidate survival and QALYs and likely decreased overall costs.

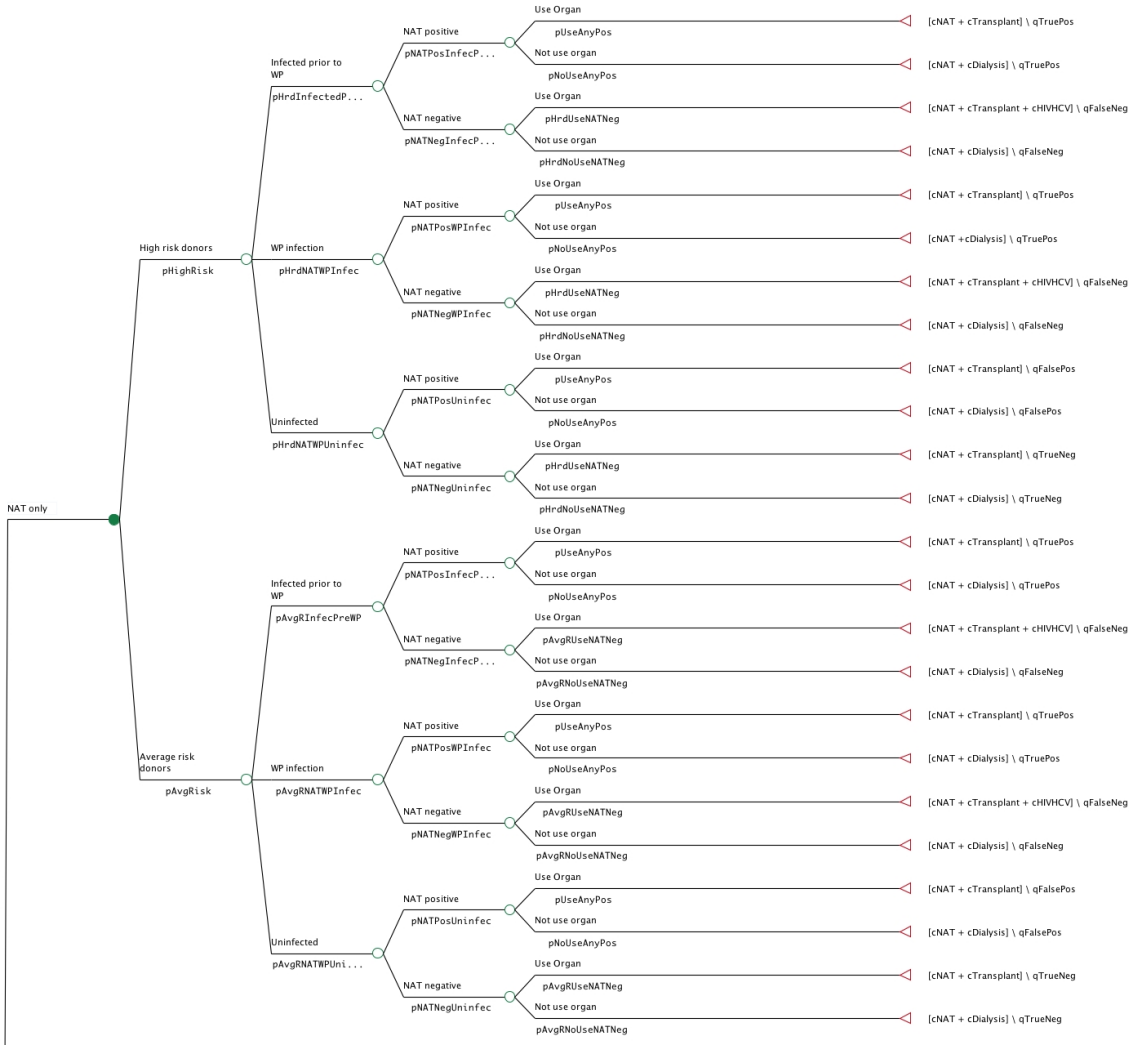
Methods

Decision Tree

A decision-tree (Figure 4) was constructed using TreeAge software (version 2014; TreeAge Software, Inc., Williamstown, MA, USA). The decision tree compared five strategies of screening organ donors for HIV and HCV: current national practice (a mixture of ELISA only, selective use of NAT with ELISA, and universal NAT with ELISA), ELISA only, selective use of NAT with ELISA, universal NAT with ELISA and NAT only (no ELISA). The model unit was a one-year amount of recovered kidneys, taken to be 15,449 in this model based on the OPTN website for recovered kidneys in 2014.[35] While 15,449 kidneys were recovered, they came from only 7,763 deceased donors meaning each donor contributed 1.99 kidneys. For this reason, the

cost of screening was based on half of the 15,449 kidneys rather than the full 15,449. This model was taken from a payer/Medicare perspective.

Figure 4 – Decision Tree. The NAT Only sub-tree is displayed.



Probabilities

A literature search was conducted to define chance node probabilities. Of note, the prevalence of pre-window period infections, window period infections and uninfected individuals among both high- and low-risk donors were taken as

"knowns" in this model as determined by the literature search. This approach allowed the use of screening test sensitivities and specificities while ranging the prevalence of infection over their confidence intervals. Decision tree probabilities, costs, QALYs and life expectancies are displayed in Table 4.

Table 4 –Decision Tree Probabilities, Costs, QALYs and Life Expectancies

Probabilities	**Value (range)**	**References**
Universal NAT	0.584 (0.466-0.684)	33,34,36
Selective NAT	0.243 (0.207-0.310)	33,34,36
ELISA Only (never NAT)	0.173 (0.036-0.310)	33,34,36
High-risk organs recovered	0.088 (0.023-0.261)	24,33

Average-risk organs recovered	0.912 (0.739-0.977)	24,33
NAT available for transplant decision	0.482 (0.364-0.632)	33,36
NAT unavailable for transplant decision	0.518 (0.368-0.636)	33,36
High-risk organs infected pre-window period	0.186 (0.159-0.215)	37
High-risk organ infected in NAT window period	0.000335911 (0.00030261-0.00037527)	16,27,38
High-risk organ uninfected (using NAT window period)	0.813664089 (0.78417473-0.84112239)	16,27,38
High-risk organ infected in ELISA window period	0.002871893 (0.00260615-0.00318866)	16,27,38
High-risk organ uninfected (using ELISA window period)	0.811128107 (0.78136134-0.83881885)	16,27,38
Average-risk organ infected pre-window period	0.0352 (0.0314-0.0397)	37
Average-risk organ infected in NAT window period	0.000023997875 (0.000012409-0.000042566)	37
Average-risk organ uninfected (using NAT window period)	0.964776002125 (0.96025743-0.96853759)	37
Average-risk organ infected in ELISA window period	0.0002125025 (0.00011257-0.00035273)	37
Average-risk organ uninfected (using ELISA window period)	0.9645874975 (0.95994727-0.96843743)	37
NAT sensitivity	0.99 (0.911-1)	39,40
NAT specificity	0.9685 (0.94-1)	39,40
NAT false positive	0.0315 (0-0.06)	39,40
NAT false negative	0.01 (0-0.089)	39,40
NAT positive in NAT window period infection	0 (N/A)	N/A
NAT negative in NAT window period infection	1 (N/A)	N/A
ELISA sensitivity	0.979 (0.929-1)	41,42
ELISA specificity	0.9992 (0.9695-1)	41,42
ELISA false positive	0.0008 (0-0.0305)	41,42
ELISA false negative	0.021 (0-0.071)	41,42
ELISA positive in window period infection	0 (N/A)	N/A
ELISA negative in window period infection	1 (N/A)	N/A
NAT and ELISA combined sensitivity	0.99 (0.911-1)	39-42
NAT and ELISA combined specificity	0.9685 (0.94-1)	39-42
NAT and ELISA combined false positive	0.0315 (0-0.06)	39-42
NAT and ELISA combined false negative	0.01 (0-0.089)	39-42
NAT and ELISA combined positive in NAT window period infection	0 (N/A)	N/A
NAT and ELISA negative in NAT window period infection	1 (N/A)	N/A
Use high-risk NAT negative organ	0.875 (0.781-0.987)	25,37
Discard high-risk NAT negative organ	0.125 (0.013-0.219)	25,37

Use high-risk ELISA negative organ	0.848 (0.703-0.954)	25,37
Discard high-risk ELISA negative organ	0.152 (0.046-0.297)	25,37
Use average-risk NAT negative organ	1 (N/A)	N/A
Discard average-risk NAT negative organ	0 (N/A)	N/A
Use average-risk ELISA negative organ	1 (N/A)	N/A
Discard average-risk ELISA negative organ	0 (N/A)	N/A
Use high-risk NAT and ELISA negative organ	0.875 (0.781-0.987)	25,37
Discard high-risk NAT and ELISA negative organ	0.125 (0.013-0.219)	25,37
Use average-risk NAT and ELISA negative organ	1 (N/A)	N/A
Discard average-risk NAT and ELISA negative organ	0 (N/A)	N/A
Use of any organ that iis NAT and/or ELISA positive	0 (N/A)	N/A
Discard any organ that is NAT and/or ELISA positive	1 (N/A)	N/A
Costs		
Nucleic acid testing	$893 ($32-$9,662)	36
Dialysis (lifetime)	$750,313 ($481,252-$1,039,155)	1
Transplantation (lifetime)	$638,947 ($393,830-$923,105)	1
Living with HIV and/or HCV (lifetime)	$218,101 ($164,182-$505,086)	43,44
QALYs (lifetime)		
True positive (dialysis)	5.2 (3.1-7.8)	45
False positive (dialysis)	5.2 (3.1-7.8)	45
True negative (transplant with uninfected organ)	12.3 (7.4-18)	45
False negative (transplant with infected organ)	11 (5.2-17.6)	45-47
Life expectancy		
Dialysis	7.5 (5-10)	2,48-50
Transplantation	15 (10-20)	2,48-50

Costs

The decision tree analysis took the perspective of the payer (i.e. Medicare). Only direct costs that would be affected by the screening strategy were included and those were the cost of the screening strategies, the cost of transplantation and

dialysis, and the cost of transplanting infected organs into recipients that then lived with a transplant and HIV and/or HCV. ELISA was taken to cost $0 as ELISA is mandated for all donors and served as a baseline. The cost of living with HIV and/or HCV contracted from a transplanted organ was set to the lifetime cost of transplantation plus the lifetime cost of living with HIV and/or HCV. All costs were converted to 2015 US$ using a 3% inflation rate.

Outcomes

QALYs were calculated by multiplying yearly utility values of dialysis, kidney transplantation and a combination of kidney transplantation with living with HIV and/or HCV by the estimated life expectancy of those on dialysis or undergoing kidney transplantation. Of note, for those who contracted HIV or HCV from a kidney transplantation, we did not factor decreased survival due to the HIV and HCV infection because the natural history of HIV and HCV infection lead to a longer life span than those on dialysis or with a kidney transplantation.[51,52]

QALY values for HIV infection were averaged from QALYs associated with people with asymptomatic HIV infection (in the first year and subsequent years), untreated and symptomatic HIV, highly active antiretroviral therapy (HAART) treatment, and AIDS.[46] QALY values for HCV infection were averaged from QALYs associated with people with mild/moderate chronic HCV, compensated cirrhosis, and decompensated cirrhosis.[47] These averaged QALYs of living with HIV and HCV infection were then multiplied by the life expectancy of a kidney transplant patient

and were used as the QALYs associated with lifelong infection due to transplantation. While the QALYs of transplantation were not factored into those QALYs associated with patients infected from a transplant, the range of QALYs for these individuals were broad enough that they encompassed any effect of QALYs that transplantation would provide. QALYs were not discounted in this model.

Sensitivity Analyses

Deterministic one-way and multi-way sensitivity analyses were performed. Analyses were carried out in TreeAge (version 2014; TreeAge Software, Inc., Williamstown, MA, USA).

Results

In terms of total cost, the least cost-effective strategy (NAT Only) cost $649,155 per organ recovered over the individual's lifetime and the most cost-effective strategy (ELISA Only) cost $645,833 per organ recovered making a difference of $3,322 per organ recovered. While the cost of screening is $6.9 million more for the NAT Only strategy, this amount only constitutes 0.07% of the total cost over an individual's lifetime as the big drivers of cost are the use or discarding of organs that leads to dialysis or transplantation. The differential sensitivity and specificity of ELISA versus NAT as well as the potentially increased use of high-risk NAT negative donors does not make a large difference in overall costs per organ recovered. Table 5 below presents the breakdown of costs of the five screening strategies and Table 6 below shows the total QALYs associated with each screening strategy.

Table 5. Cost Breakdown Between the Five Screening Strategies

Strategy / Cost	NAT Only	ELISA Only	Selective NAT with ELISA	Universal NAT with ELISA	Current practice
Total Cost*	$10,028,796,645	$9,977,479,758	$9,977,655,615	$10,005,787,650	$9,991,573,732
Cost of screening	$6,897,978	$0	$607,022	$6,897,978	$1,695,358
Cost of using false negative organs	$1,724,692	$4,627,560	$4,080,863	$3,228,377	$3,677,590
Cost of transplantation	$9,015,765,440	$9,287,267,541	$9,286,604,695	$9,156,403,529	$9,210,681,886
Cost of dialysis	$1,004,408,535	$685,584,656	$686,363,034	$839,257,766	$775,518,898
Total cost difference from ELISA Only	$51,316,887	-	$175,857	$28,307,892	$14,093,974
Cost per organ recovered	$649,155	$645,833	$645,845	$647,666	$646,746
Cost difference from ELISA Only per organ recovered	$3,322	-	$12	$1,833	$913

* based on 15,449 recovered organs

Table 6 - QALYs Associated with Each Screening Strategy

Strategy / QALYs	NAT Only	ELISA Only	Selective NAT with ELISA	Universal NAT with ELISA	Current practice
Used	173,547	178,756	178,747	176,245	177,288
Discarded	7,914	5,949	5,836	6,896	6,475
Total QALYs	181,461	184,705	184,583	183,141	183,762

The screening strategy with the lowest effectiveness (NAT Only) is associated with 173,547 QALYs over the individuals' lifetime and the most effective (ELISA Only) is associated with 178,756 QALYs. The difference in QALYs is 5,209 (for the 15,449 recovered organs per year over the course of the patients' lifetime) which is the lifetime QALYs associated with 423 transplanted waiting list candidates.

Another matter to consider is the loss of QALYs associated with the false positives (the difference in QALYs between transplantation and dialysis). In order to give a full accounting of each strategy's misclassification, the false negatives need to be evaluated as well (Table 7). The loss of QALYs associated with false positives were calculated by multiplying the absolute number of false positives per year based on 15,449 organs recovered and then multiplying by the difference in QALYs between dialysis and transplantation. Of note, even using false negative organs and transmitting HIV and/or HCV resulted in higher QALYs than remaining on dialysis.

Table 7 - False Positive and False Negative Counts by Screening Strategy

Strategy / QALYs	NAT Only	ELISA Only	Selective NAT with ELISA	Universal NAT with ELISA	Current practice
False positive	-3,287.52	-83.46	-199.68	-1,627.81	-1,013.61
False negative	37.18	99.75	87.96	69.59	79.27
Total QALYs lost/gained due to screening test misclassification	-3,250.34	16.29	-111.72	-1,558.22	-934.34

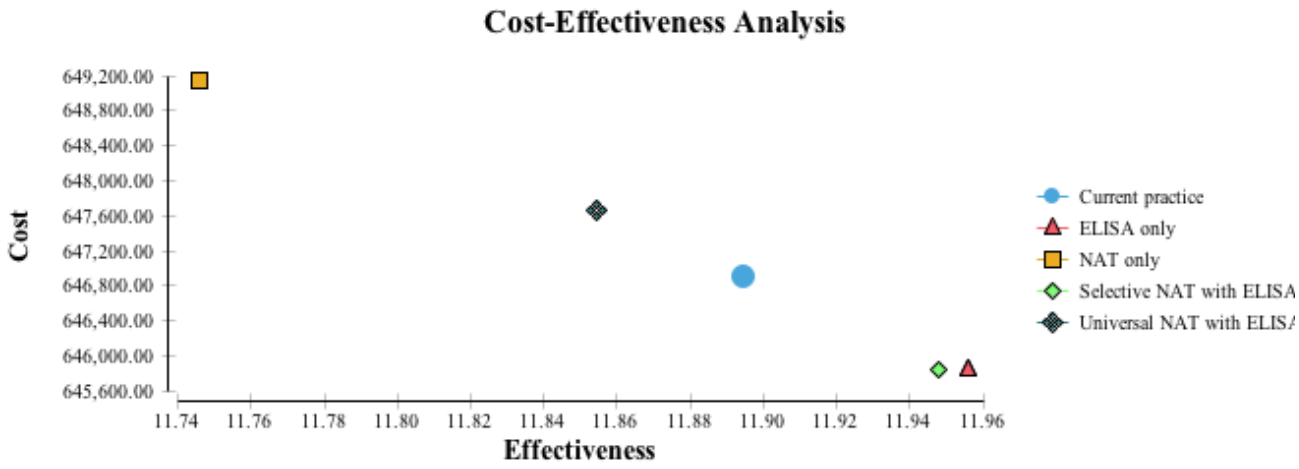
The NAT Only strategy lost the most number of QALYs while the ELISA Only strategy actually gains QALYs as there are more QALYs associated with its false negative rate than false positive rate.

Cost-Effectiveness

The strategy of using ELISA Only as a screening tool for CDC HRDs is the most cost-effective strategy and dominates all other strategies (meaning every other strategy is more expensive and produces less QALYs) (Figure 5). The ELISA Only strategy had the advantage of having a $0 cost associated with it since ELISA is required of all recovered organs for transplantation and did not represent an incremental increase in cost for any of the strategies and was therefore set as the baseline. When using the Current Practice strategy as a point of reference, it can bee seen that employing a Selective NAT with ELISA strategy moves in a more cost-effective direction rather than the Universal NAT with ELISA or NAT Only strategy.

The cost per QALY of the strategies varied from $55,816 (ELISA Only) to $57,787 (NAT Only) and all were close to the Current Practice screening strategy cost (and presumably willingness to pay) of $56,358. These values fall very close to the historic and still popular willingness to pay threshold of $50,000/QALY although that value is outdated and of dubious origin.[53] The cost-effectiveness of the screening strategies were also close to cost-effectiveness values for kidney transplantation in the literature ($17,000-$60,000[15,54,55]).

Figure 5. Cost-effectiveness of Five Screening Strategies for Infectious Risk in Deceased Donor Kidneys (Cost and Effectiveness per Organ Recovered)



Incremental cost-effectiveness ratios (ICERs; the difference in cost between two strategies divided by the difference in QALYs) with the ELISA Only as the baseline as

well as another set of ICERs using Current Practice as the baseline are shown in Table 8 below. All costs and QALYs were totals over the individual's lifetime.

Table 8 - Calculation of ICERs Using ELISA Only and Current Practice as Reference Strategies

Strategy / **ICERs**	NAT Only	ELISA Only	Selective NAT with ELISA	Universal NAT with ELISA	Current Practice
Total cost per recovered organ	$649,155	$645,833	$645,845	$647,666	$646,746
Incremental cost	$3,322	-	$11	$1,832	$912
QALY per recovered organ	11.75	11.96	11.95	11.86	11.90
Incremental QALY	-0.21	-	-0.01	-0.10	-0.06
ICER	-$15,815	-	-$1,443	-$18,100	-$14,946
Incremental cost	$2,409	-$912	-$901	$920	-
Incremental QALY	-0.15	0.06	0.05	-0.04	-
ICER	-$16,171	-$14,946	-$16,950	-$22,889	-

With ELISA Only as the reference strategy, the Universal NAT with ELISA has the largest magnitude ICER at -$18,100, meaning that the strategy costs $18,100 to lose every QALY less than the QALYs associated with the ELISA Only strategy. Of note, the Current Practice has an ICER of -$14,946 meaning that Medicare currently pays $14,942.69 to lose every QALY when compared to an ELISA Only screening strategy. With ELISA Only as the baseline, every other strategy pays to lose QALYs.

With the Current Practice as the baseline, the NAT Only and Universal NAT with ELISA strategies pay to lose QALYs while the ELISA Only and Selective NAT with ELISA strategies cost less money to gain QALYs. So while ELISA Only is a dominant strategy in this study, if one assumes that NAT will inevitably be used (making the ELISA Only strategy a non-viable strategy) and uses the Current Practice as the baseline in the ICERs, then it is clear that moving away from the Current Practice and toward Selective NAT with ELISA would be the most cost-effective choice.

False Positives and False Negatives

Both NAT and ELISA are associated with false positive and false negative rates and their differential number of each affects both costs and QALYs. Since the false positive rate of NAT is of concern, Table 9 below reports the differential number of true and false negatives and positives of the five screening strategies.

Table 9 - Test Performance. Number of True Negatives, True Positives, False Positives and False Negatives by Screening Strategy (Organs Used or Discarded Based on Test Result of the Screening Tool)

Strategy / Number and type of organs	NAT Only	ELISA Only	Selective NAT with ELISA	Universal NAT with ELISA	Current practice
True negatives	14,236	14,682	14,667	14,467	14,553
Use	14,102	14,514	14,516	14,316	14,399
Discard	134	167	151	151	154
True positives (discard, remain on dialysis)	741	733	734	737	735
False positives (discard, remain on dialysis, lost QALYs)	463	12	28	229	143
False negatives	8	22	20	16	17
WP use	1	6	5	4	4
WP discard	0.1	0.6	0.3	0.3	0.4
Use	7	15	14	11	12
Discard	0.3	0.8	0.6	0.6	0.6
Total organs used	14,110	14,535	14,535	14,331	14,415
Total organs discarded	1,338	913	914	1,118	1,033

* WP = window period

When comparing the NAT Only and ELISA Only strategies, the major differences in organ usage comes in the largest false positive sum of organs of the NAT Only strategy leading to discarding uninfected organs with an associated loss of QALYs (NAT discards just over 450 more uninfected organs than ELISA Only, which has the

lowest numbers of false positives). The 450 extra uninfected organs that are discarded when using a NAT Only as compared to ELISA Only strategy has a monetary cost equal to the number of discarded, uninfected organs times the difference in lifetime dialysis cost and lifetime transplantation cost, or $50,114,700.

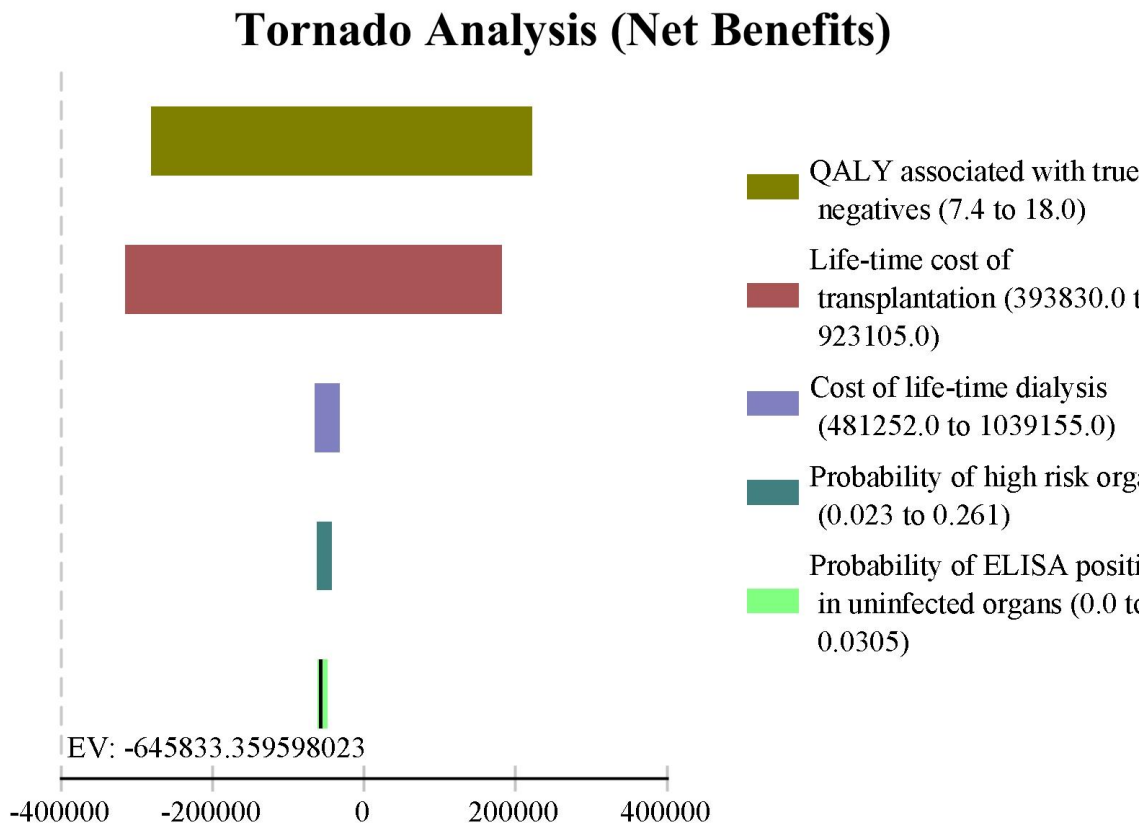
The other area of large discrepancy is the false negative rate which leads the NAT Only strategy to transplant the lowest number of infected organs out of the five screening strategies and ELISA Only to transplant the largest number of infected organs out of the five screening strategies (ELISA Only will transplant 14 more infected organs than NAT Only per year assuming 15,449 recovered kidneys). The incremental cost associated with the 14 extra infected organ transplants under the ELISA Only strategy has a monetary cost equal to the number of excess false negatives (14) times the difference in lifetime dialysis cost and lifetime transplantation with contracted HIV and/or HCV, or $1,494,290. False positives carry 33.5 times more of a monetary penalty than false negatives.

Sensitivity Analyses

One-way sensitivity analyses of the twenty most important variables revealed no change in the order of cost-effectiveness of the five strategies except for ELISA Only dominance changing to Selective NAT with ELISA dominance when NAT specificity was 99.4% or higher as well as for ELISA specificity less than 97.3%.

A tornado diagram of net monetary benefits is shown in Figure 6 below demonstrating the five most influential variables in determining comparative strategy cost-effectiveness. The QALYs associated with uninfected organ transplantation and the lifetime cost of transplantation were the most influential variables in determining which screening strategy was most cost-effective. Of note, the variables dealing with the concerns for NAT of availability and cost were not important while the false positive rate (reflected as false positive rate of ELISA in the tornado diagram) was an important factor.

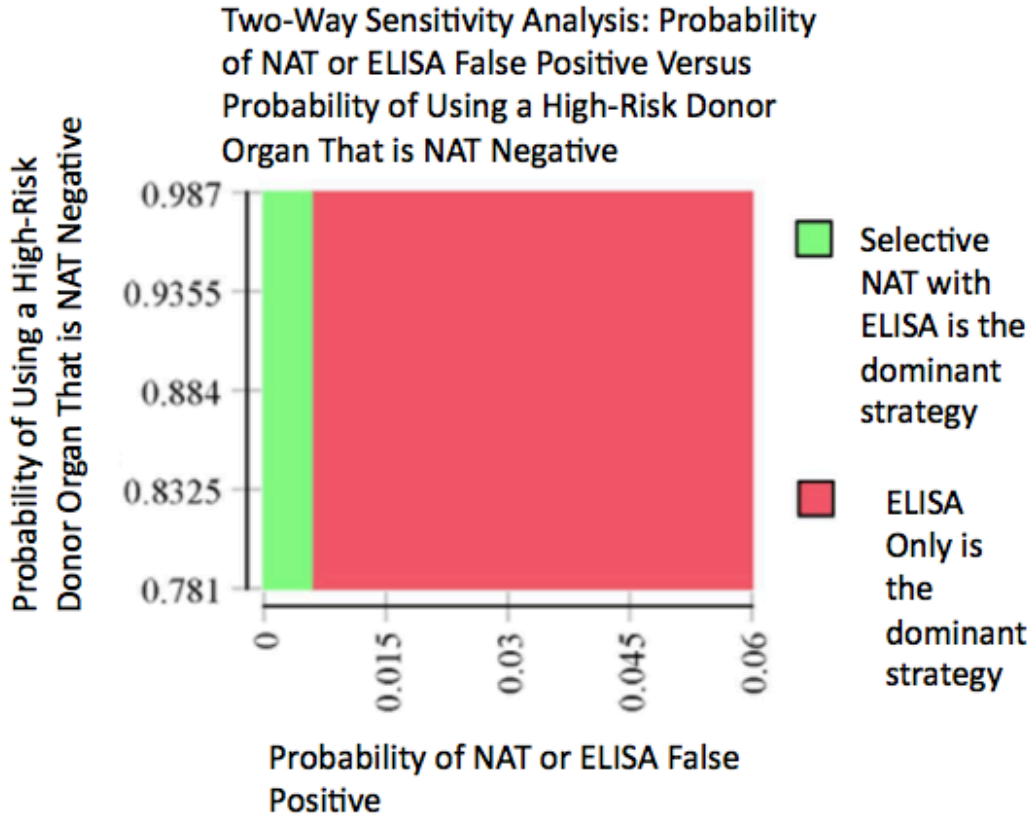
Figure 6 - Tornado Diagram of the Five Most Influential Variables. The solid vertical bar in the "Probability of ELISA positive in uninfected organs" (false positive rate based on specificity) demonstrates point of comparative cost-effectiveness strategy change.



Two-way sensitivity analyses were conducted for the four parameters of most interest with NAT testing, namely the cost, availability, and specificity (false positive rate) of NAT as well as the use of NAT negative organs. In all these combinations, ELISA Only remained the dominant strategy except when Selective NAT with ELISA became dominant in the instances where NAT specificity was at or above 99.4%

when comparing the use of NAT negative organs and cost of NAT (when the cost of NAT was somewhere between $16 and $1300). Also, the NAT Only strategy became dominant over the ELISA Only strategy when comparing NAT specificity with NAT availability when NAT specificity was at 99.4% or higher. Figure 7 shows the multi-way sensitivity analysis between the NAT false positive rate and the use of NAT negative organs.

Figure 7 – Two-Way Sensitivity Analysis: Probability of NAT or ELISA False Positive Versus Probability of Using a High-Risk Donor Organ That is NAT Negative



Discussion

When considering the ELISA Only strategy a non-viable option in terms of screening alternatives due to the very unlikely occurrence of all OPOs ceasing to use NAT as a screening tool, Selective NAT with ELISA is the most cost-effective screening strategy of the remaining four strategies. The more NAT is implemented (i.e. Universal NAT with ELISA and NAT Only strategies), the less cost-effective the screening strategy becomes due to increased cost and decreased QALYs.

The cost-effectiveness ratio of the Selective NAT with ELISA strategy is $55,820 which is comparable with a prior study of the effect of strategies accepting or discarding all HRDs.[28] Compared to the Current Practice, Selective NAT with ELISA has the most favorable ICER at a cost savings of $16,950 for every QALY gained over the Current Practice. While both Universal NAT with ELISA and NAT Only strategies have negative ICERs as well, their ICERs are the result of increased cost for less QALYs. While Selective NAT with ELISA has a budget impact in terms of paying for NAT that is 11 times less than Universal NAT with ELISA or NAT Only, the cost of paying for the NAT tests only accounts for 0.07% of the total cost of the overall strategies and does not change the overall costs more than $3,322 per organ recovered.

An advantage of the Selective NAT with ELISA strategy over the Universal NAT with ELISA or NAT Only strategy is that Selective NAT with ELISA has over 450 fewer false positives (which lead to the discard of uninfected organs with concomitant loss

of survival and QALYs and increased cost of care on dialysis) compared to NAT Only and 115 fewer false positives that the Current Practice. This is at the expense of having 11 more false negatives (transplanting infected organs) than NAT Only or 3 more than the Current Practice.

Overall, Selective NAT with ELISA will lead to the most transplanted organs and fewest discarded organs. In terms of QALYs, Selective NAT with ELISA has the highest number of associated QALYs (outside of the non-viable screening option of ELISA Only) and the least amount of QALYs discarded. When summing up the lost QALYs due to false positives (difference between QALYs of dialysis and transplantation) and accounting for the QALYs tied up in false negatives (all QALY differences were gains associated with being transplanted with an infected organ over dialysis), Selective NAT with ELISA lost the least amount of QALYs outside of the ELISA Only strategy. In summary, Selective NAT with ELISA is the most cost-effective (outside of ELISA Only) screening strategy and is associated with more transplanted organs, increased survival, most QALY gains, least QALY losses, and least discarded organs at the cost of 3 more infected organs transplanted over the Current Practice.

There is a general public, as well as physician, fear of transmitting an infectious disease to a transplant recipient. Not only is a physician's creed to do no harm, but there is concern about how a new infection will act in a newly and sustained immunocompromised patient. For these reasons, UNOS has adopted the CDC HRD

criteria to label organs for closer scrutiny that may be infected with HIV and/or HCV and physicians have subsequently been more reluctant to use these organs.[24,25] While it is known that HRD organs are at risk, it has been shown that that risk is still relatively small[16,24,27] and so the lower use of HRD organs represents a discarded pool of mostly uninfected organs that would serve to benefit those on the transplant waiting list. A potential solution to the discarding of uninfected HRD organs has been to use NAT which would more accurately identify uninfected organs and thereby increase the willingness of transplant surgeons to use the donor organs.[25] However, there has been a reluctance to accept universal NAT due to recent reports pertaining to its high false positive rate, cost and laboratory turn-around time.[16,32,33]

False positive rates for NAT have been reported in the 9-57% range although these quality control studies did not include HIV and were published from 1993-1997.[31] Based on current NAT tests, we used a value of 96.85% for NAT specificity which corresponds to a false positive rate of 3.15%.[56]

As for the costs of NAT, a 2009 survey of OPOs revealed widely variable costs depending on day or night testing, the volume of tests run and transportation costs. The costs (including the test and transportation) ranged from $32 to $9,662 (in 2015 US$) with a median cost of US$893.[32] According to our personal communication with the Maryland OPO (personal correspondence, Karen Kennedy, The Living Legacy Foundation of Maryland, March 3, 2013), the cost of NAT was $75 each for HIV and HCV with no other associated direct costs (these NATs were

performed in the same laboratory and at the same time as other screening tests so there was no additional transportation or handling costs). The Maryland OPO reported cost of $75 is about 10% of the reported costs from the 2009 survey.

The reportedly slow NAT turn-around time has been due to two factors: the time needed to perform the test and the need, in certain cases, to send the test to a distant laboratory since local laboratories did not perform NAT. Of the OPOs that responded to a 2009 survey, less than half reported always receiving NAT results within 12 hours of blood draw.[32] In fact, according to a 2008 survey of 58 OPOs, 21% of OPOs stated that they would not be able to comply with mandatory NAT of organ donors due to NAT result turnaround time.[34] As NAT becomes more common and the technology becomes less expensive, it is likely that the same laboratories that perform donor-screening tests will include NAT as one of their panel and thereby reduce the cost and turnaround time substantially. The question then remains how best to use NAT as it becomes a much more accepted and utilized screening test with the lasting cause for concern being its false positive rate.

While the actual risk of WP infection in HRDs is low, the risk still exists as evidenced by the 2007 transmission of HIV and HCV from one donor to four recipients due to such a WP infection.[21,22] However, it should be noted again that living with HIV and/or HCV is associated with more QALYs than remaining on dialysis and the subsequent lifespan of those with the infections are longer than the lifespan of those under treatment for ESRD.[46,47] So while it is never desirable to transmit infectious

disease via solid organ transplantation, the fact remains that even in the face of transmitted infection, the patient is usually still better off in terms of QALYs and/or survival. This means that the pursuit of zero transmitted infections is likely not desirable at the cost of too many lost uninfected organs, QALYS and survival so that NAT should be used more sparingly than universally.

However, when dealing with HRDs, the individual transplant candidate interests would best be served by addressing two items: first, proper informed consent and second, assuring the patient has a detailed understanding of whether they belong to a patient subgroup that benefits from use of HRDs, even if receiving HIV and/or HCV via transplantation. In terms of informed consent, UNOS mandates special informed consent (SIC) from patients using HRDs. While one study discovered no decrease in HRD utilization when using SIC[57], informed consent might still be served by presenting risk in everyday terms that patients might be better able to grasp. For example, one academic study related the risk of death from contracting AIDS from an HRD to common medications, occupations, modes of transportation and recreational activities (e.g. the risk of death from AIDS from HRDs was less than the risk of death from the use of Vioxx, having an occupation as a tree feller, riding a motorcycle and just more than rock climbing).[58] Second, in terms of understanding subgroups that benefit from accepting HRDs, a recent study explored via Markov modeling and Monte Carlo simulation 230,400 patient phenotypes and generated an online tool to assess subgroup risk and benefit of using HRDs based on ten recipient characteristics and two donor characteristics.[30]

There are several limitations in this analysis. First, the probabilities, utilities and costs were drawn from different populations from the literature. As transmission of disease via HRDs is so uncommon, we feel that literature-based values from closely related populations were appropriate. Secondly, there was no literature on the QALYs of those kidney transplant patients infected by false negative HRD organs but this was addressed by averaging a wide range of proxy QALYs in this analysis.

Third, the willingness of transplant surgeons to use HRDs come from a survey conducted in 2008[25] and while the difference in becoming a high-utilizer of HRDs due to the use of NAT was not found to be statistically significant in kidney transplantation, this analysis assumed statistical significance. This approach avoided the possibility of NAT resulting in decreased HRD use and the results of this study showed that even if negative NAT did significantly increase HRD use, it was still did not overcome the negative effect of the NAT false positive rate. Fourth, we did not address discordant results between NAT and ELISA but since these instances are very unlikely, it likely would have no effect on our results. Fifth, for the simplicity of the model, the cost and loss of QALYs related to dialysis due to false and true positives were overestimated as a true positive or false positive was assigned a lifetime cost and QALY of dialysis although many of those patients would get transplanted with an uninfected organ in subsequent years. This approach made the difference between screening strategies more pronounced but should have no effect on their relative cost-effectiveness.

Sixth, our model predicts a total of 749 infected organs (253 from HRDs and 496 from average risk donors resulting in 8-22 transplants of infected organs) with an additional 0.3-4 for WP infections associated with NAT or ELISA assuming 15,449 organs recovered. According to the OPTN/SRTR database for 2013, a total of 3,638 high-risk donor organs were recovered with 3,159 of them being transplanted (an 86.8% utilization rate) which left 479 high-risk organs discarded (unpublished data, February 28, 2015). In this paper, we are arguing that there are uninfected HRDs that are disposed of in the 479 that were discarded in 2013, yet our expected number of infected organs is higher than this. Clearly there would have to be in excess of 270 infected organs transplanted for there to be only 479 HRDs discarded, yet during the past twenty years, there have been at least 7 reported incidents of viral disease transmission from a solid organ donor to transplant recipients[21-23] leaving a large gap between expected and observed infection transmission rate.

The reason for the gap between expected and observed high-risk organ infection transmissions can be several-fold. First, those deciding to donate organs may self-select in terms of those with HIV or HCV or those highly suspicious that they may have HIV and/or HCV donate at much lower rates than those who are not infected or are not suspicious that they have HIV and/or HCV. Another possibility is that the risk of transmission of HIV and/or HCV from a donated organ is very low.[59] In order to be conservative in this paper, we assumed 100% transmission of infection from infected organs to recipient as the tolerance of transmission of infection via

transplantation is extremely low in practice and public opinion. A third option is that transmitted infections are not discovered prior to patient death or are not reported as the infection may have been assumed to be from other sources (e.g. blood transfusions) rather than the transplant. A recent paper evaluating the use or discard of HRD organs estimated 2-9 WP infection transmissions per 1000 recipients. [28] Also of note in that study was that transplanting all the HRDs lead to a lower acquired infection rate than in the discard arm as the risk of acquiring HCV on dialysis was greater than the risk of transplanting all of the HRD organs.[28]

In conclusion, CDC HRD organs represent a category of organs whose increased use could lead to additional uninfected kidneys being added to the donor pool each year. The current, cumulative, individual HRD screening strategies employed by OPOs do not provide a cost-effective use of these organs. Across all OPOs, the collective decisions between using universal NAT, selective NAT and ELISA only strategies do not balance efficiently the tradeoffs between NAT cost, NAT availability, the effect of NAT increasing transplant willingness to use HRDs and the effect of the false positive rate associated with NAT. In addition, the Dartmouth Institute for Health Policy and Clinical Practice, the New England Healthcare Institute, McKinsey consulting and Thomson Reuters have all estimated that 30% of the national spending in health care could be eliminated by reducing unwarranted variation in healthcare practices (lowering spending to the level of low spending regions while maintaining equivalent quality).[60] So by identifying the best strategy to screen for infections of HIV and HCV in donor kidneys, a national evidence-based policy could serve to cut wasted costs while improving or

maintaining the quality of health care delivered. Selective NAT with ELISA is the most reasonable and cost-effective screening strategy and the selective NAT use should be determined at a national level. NAT use should be selective as the ratio of its discovery of a false negative ELISA WP infections to its mislabeling of false positives is very unattractive and detrimental to those on the waiting list. While transplant physicians do not want to transmit infections via solid organ transplantation and they want to keep such transmissions from being sensationalized in the media by decreasing such transmissions, their obligation is also as stewards of the waiting list and establishing guidelines to such an end is paramount. As we know that infectious risk differs greatly (to over a thousand-fold) even between high-risk behaviors,[16,24,27] we believe that a more nuanced selective use of NAT should be established based on risk behavior and specific candidate population. This is especially important as the transplant community moves toward including more behaviors into the high-risk category (such as recent sexually transmitted disease, recent hemodialysis, tattooings from a non-professional, and body piercings)[61,62] which will lower transplant surgeon utilization of such organs and encourage more NAT use which will lead to more discarding of uninfected organs due to the false positive rate of NAT. We believe a national policy of selective NAT use will best serve the ESRD community.

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APPENDIX 1. Detailed Calculations for Select Decision Tree Inputs

NAT Availability

For this value, we used the percentage of times that the NAT is "always" available for the transplant decision. The two papers used did not just categorize "always" and "never" having the NAT results by the time of the transplant decision but they also included the percentage of times that the NAT results are available <10% of the time, 10-25% of the time, 25-50% of the time, 50-75% of the time and 75-99% of the time. The goal of this study was to evaluate the effects of having NAT available, so we discarded the other categories since even if there was a 1% that the results of the NAT would not be back, that would violate the premise of this study in terms of using NAT for the transplant decision.

NAT available for transplant decision

1. HIV: The average of 0.364[1] and 0.632[2] in always having the NAT results available at the time of the transplant decision was 0.498. The range was established by using the lowest reported value, 0.364[1], and the highest reported value, 0.632.[2]

2. HCV: The average of 0.375[1] and 0.589[2] in always having the NAT results available at the time of the transplant decision was 0.482. The range was established by using the lowest reported value, 0.375[1], and the highest reported value, 0.589.[2]

3. Combined: To be conservative, the lowest point value between HIV and HCV was used as the combined point value, 0.482.The range was established by using the lowest reported value, 0.364[1], and the highest reported value, 0.632.[2]

Organ Use

The probability of organ use based on the use of NAT with ELISA or just ELISA was taken from one paper published in 2009.[3] A national survey was conducted between January and April of 2008 assessing the use of high-risk donor organs among transplant surgeons with hierarchical models examining the association between OPO NAT performance and high-risk donor use among that OPO's transplant surgeons. NAT performance was associated with a significantly higher odds of high-risk donor organ use when looking at pancreas, kidney, liver and simultaneous pancreas and kidney transplant (significance was lost when only looking at kidney use except in the use of commercial sex worker risk organs for HIV and HCV and for intravenous drug use risk kidneys for HIV). Specifically, the increase in odds was measured for those who were "high utilizers," or those who responded that they accepted more than 10% of "otherwise standard criteria offers from donors of this type" (high utilization was assessed by each of the seven high-risk behaviors) in the OPO's that did not always use NAT as opposed to those OPO's that always used NAT. Of note, there was variation between HIV and HCV and the type of high-risk behavior as to whether those organs were used at greater frequency or not with NAT testing (e.g. organs exposed to HIV were rarely used and NAT testing did little to increase utilization of these organs). According to the article, NAT utilization increased the odds of surgeons being "high utilizers" of high-risk donor organs at risk for HIV by 1.52 (0.74-3.12) and for HCV by 1.30 (0.61-2.75). We, however, turned these insignificant results to significant results by not accepting that NAT use would decrease kidney utilization and making the ranges instead for HIV 1.52

(1.01-4.30) and for HCV 1.30 (1.21-4.29). We felt comfortable doing this as we planned to explore the magnitude of change in high-risk organ utilization due to NAT in the sensitivity analyses in order to determine the value at which the increased utilization might affect the results of the study.

The baseline utilization rate across the country of high-risk organs was determined by examining the OPTN/SRTR database for 2013. That year, a total of 3,638 high-risk donor organs were recovered with 3,159 of them being transplanted (an 86.8% utilization rate) which left 479 high-risk organs discarded (unpublished data, February 28, 2015). The range of utilization was then taken as 10% more or less than 86.8%.

In order to determine the increase in probability of using high-risk organs with the use of NAT (or the decrease probability of using high-risk organs when using only ELISA), the current probability of using a high-risk organ according to the data from the SRTR for 2013, 86.8%, was converted to odds by, "odds = [probability/(1-probability)]=0.868/0.132=6.58". This value was then multiplied by the odds ratio point value and range for the increased use of HIV and HCV when using NAT. These odds were then converted back to probabilities by using the equation, "probability=[odds/(1+odds)]." These differences were then added to the baseline probability of 86.8% to determine the increase in probability associated with using NAT or were subtracted from the baseline probability of 86.8% to determine the decrease in probability associated with using ELISA only.

Of note, since the increase and decrease in utilization probability based on using NAT or using only ELISA could only affect a certain group of OPO's (e.g. the OPO's that always use NAT could not increase their probability of using high-risk organs by using NAT because they already always use NAT), the increase and decrease in utilization probability was multiplied by the percentage of OPO's that could be affected by a change in NAT usage policy. This meant that the increase in probability of high-risk organ usage when using NAT was multiplied by 0.25 (with a range of 0 to 0.33) to reflect the pool of utilizers that might be affected by NAT use (68.4% of OPO's already always use NAT and 13.8-18.2% of OPO's already use NAT selectively meaning only around 25% of OPO's could be affected by changing their NAT policy from ELISA only). By corollary, the decrease from the baseline utilization of high-risk organs of 86.8% when using only ELISA was multiplied by 0.75 (with a range of 0.68-0.80) to establish the decreased probability of high-risk kidney use since using ELISA only would only affect those OPO's who always used NAT (68.4%) or a portion who only selectively used NAT (13.8-18.2%).

Tables 10-11 show the decrease in use of high-risk organs at risk for HIV and HCV, respectively, when using ELISA only from the baseline utilization rate of 86.8% as determined from the OPTN/SRTR 2013 data. Tables 12-13 show the increase in use of high-risk organs at risk for HIV and HCV, respectively, when using NAT from the baseline utilization rate of 86.8% as determined from the OPTN/SRTR 2013 data.

Table 10 - Decrease in Use of Kidneys at High-Risk for HIV When Using ELISA Only

Probability of organ utilization	68% NAT effect	75% NAT effect	80% NAT effect
0.868	0.840 (0.801-0.867)	0.837 (0.794-0.867)	0.835 (0.790-0.867)
Lower bound - 0.781	0.753 (0.714-0.780)	0.750 (0.708-0.774)	0.748 (0.703-0.780)
Upper bound - 0.955	0.927 (0.888-0.954)	0.924 (0.882-0.954)	0.922 (0.877-0.954)

Table 11 - Decrease in Use of Kidneys at High-Risk for HCV When Using ELISA Only

Probability of organ utilization	68% NAT effect	75% NAT effect	80% NAT effect
0.868	0.850 (0.801-0.854)	0.848 (0.794-0.853)	0.846 (0.790-0.852)
Lower bound - 0.781	0.763 (0.714-0.767)	0.761 (0.708-0.766)	0.759 (0.703-0.765)
Upper bound - 0.955	0.937 (0.888-0.941)	0.935 (0.882-0.940)	0.933 (0.877-0.939)

Table 12 - Increase in Use of Kidneys at High-Risk for HIV When Always Using NAT

Probability of organ utilization	0% NAT effect	25% NAT effect	33% NAT effect
0.868	0.868 (0.868-0.868)	0.878 (0.868-0.892)	0.882 (0.868-0.900)
Lower bound - 0.781	0.781 (0.781-0.781)	0.791 (0.781-0.806)	0.794 (0.781-0.813)
Upper bound - 0.955	0.955 (0.955-0.955)	0.965 (0.955-0.980)	0.968 (0.955-0.987)

Table 13 - Increase in Use of Kidneys at High-Risk for HCV When Always Using NAT

Probability of organ utilization	0% NAT effect	25% NAT effect	33% NAT effect
0.868	0.868 (0.868-0.868)	0.875 (0.873-0.892)	0.877 (0.875-0.900)
Lower bound - 0.781	0.781 (0.781-0.781)	0.788 (0.786-0.806)	0.790 (0.788-0.813)
Upper bound - 0.955	0.955 (0.955-0.955)	0.962 (0.960-0.980)	0.964 (0.962-0.987)

For the combined HIV and HCV values, we referred to the data that 97% of the NAT pre-window period infections were HCV and 3% were HIV.[4] We used this data to weight the increased or decreased use of high-risk organs based on use of NAT or not as 97% of the

increased or decreased probability of using an HCV organ and 3% of the increased or decreased probability of using an HIV organ.

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CHAPTER FOUR – MANUSCRIPT #3

Identifying Appropriate Recipients for High Kidney Donor Profile Index Deceased Donor Kidneys: A Cost-Effectiveness Analysis [3]

Abstract

Introduction: With the increasing disparity between transplant candidate numbers and kidneys available in the donor pool there has been interest in identifying transplant candidate subpopulations that would benefit from the utilization of high KDPI kidneys as a means to increase the donor kidney pool.

Objectives: To establish the cost effectiveness of utilizing high KDPI kidneys in various transplant candidate subpopulations.

Methods: A Markov model was developed, based on SRTR data from 2002-2011, that allowed 129,024 patient phenotypes to be evaluated as to their survival and QALY gain associated with accepting a deceased donor kidney with a KDPI of 51-60, 61-70, 71-80,

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81-90 or 91-100. The same model also explored the cost effectiveness, in cost per QALYs, of transplanting these high KDPI organs into the specific patient phenotypes.

Results: Cost-effectiveness, in cost per QALY gained, across all 129,024 phenotypes ranged from -$54 million to $43 million with a mean of -$154,600. Seventy-seven percent of the scenarios evaluated resulted in cost savings per QALY gained. 56% of the phenotypes had positive additional survival and 87% of the phenotypes had cost savings. The main drivers of increased survival and QALYs stratified by KDPI were waiting time, PRA, and prior transplantation.

Conclusions: Acceptance of even the highest KDPI kidney offers can confer survival benefit, QALY benefit and cost savings in some transplant candidate subgroups. It is important to identify and recognize these subgroups so that the kidney donor pool can be used more efficiently.

Introduction

The mismatch between donor kidneys available for transplantation and the number of transplant candidates on the waiting list continues to grow. From 2011-2012, there was an increase of 7% in transplant candidates on the waiting list accompanied by a decrease in transplants leading to a disparity where demand was 2.7 times larger than the supply of kidneys.[1] A number of initiatives have been pursued in order to increase and better utilize the scare resource of donor kidneys. One such initiative has been to classify kidneys outside of the standard criteria for transplantation in order to evaluate how those kidneys might be used to expand the donor pool by finding appropriate subpopulations of waiting list candidates for their use. From 2002 until 2012, the prevailing classification scheme for donor kidney quality and usage was the standard criteria donor (SCD) versus expanded criteria donor (ECD) [2] and since 2012, a more granular scale, the kidney donor profile index (KDPI), has been used[2].

In an effort to avoid discarding potentially useful ECD kidneys, multiple studies have explored the benefit of transplant candidates accepting ECD kidneys rather than remaining on the waiting list. One such study found that the adjusted long term relative mortality risk at 3 years was 60% lower for ECD kidney recipients than for those remaining on the waiting list (RR 0.4, 95% CI 0.37-0.44) and that ECD kidney offers were especially beneficial in specified subpopulations of waiting list candidates.[3] This type of research and promoting of the use of ECD kidneys was successful as from the end of 2002 when the separate ECD waiting list was created to 18 months later, there was a 15% increase in number of ECD transplants.[4]

A new, more granular deceased donor kidney quality scale, the KDPI, was introduced in 2005 since the binary SCD/ECD classification system was found to misclassify donor kidneys in both directions.[2] With a more granular classification system of donor kidneys, the same type of research was carried out to evaluate which subgroup of transplant candidates would benefit from high KDPI kidneys (graft survival decreases with increasing KDPI[5]) so as to avoid discarding potentially useful organs (donor kidneys with a KDPI score over 80 have a discard rate of approximately 50% in the U.S.[6]). A recent study found that recipients of KDPI organs of 71-80, 81-90, 91-100 reached break even points of cumulative survival at 7.7, 18, and 19.8 months after transplantation and had survival benefit thereafter.[7] What is not known is the cost-effectiveness of transplanting high-KDPI kidneys while evaluating subpopulations defined by a greater number of patient parameters.

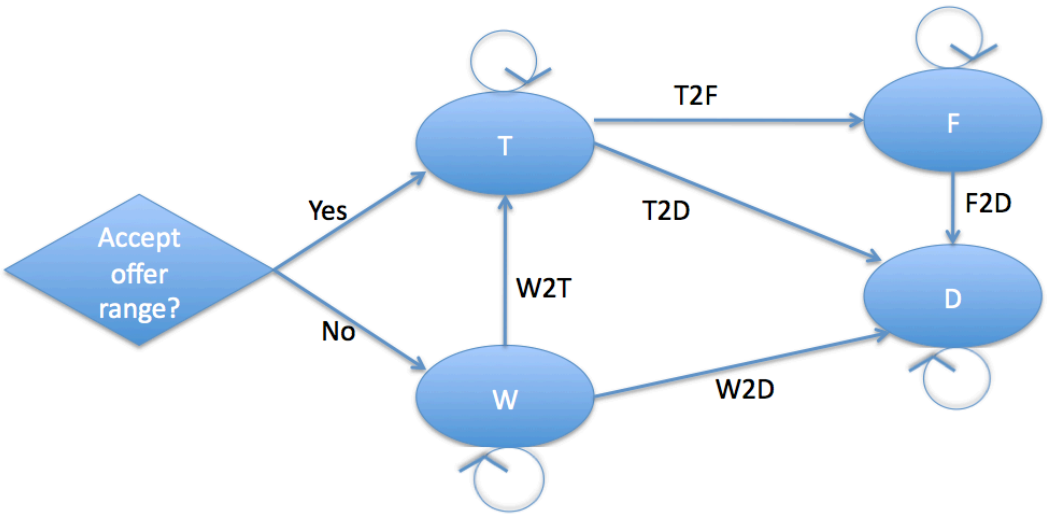
The objective of this study was to evaluate the survival and quality adjusted life year (QALY) benefits that high KDPI kidneys offer to specific subpopulations on the waiting list as well as the costs associated with the transplantation of these kidneys. We believe that by showing a survival and QALY benefit at incrementally lower costs as compared to these patients remaining on the waiting list in certain subpopulations, we can encourage the appropriate use of high KDPI kidneys and thereby avoid them being discarded or further marginalized by increased cold ischemic time due to their offers being turned down before finally being accepted. By identifying and encouraging a more efficient use of the deceased donor kidney pool, we hypothesize that the donor pool can

effectively be increased with greater benefits to those on the waiting list and at decreased cost to society.

Methods

A Markov decision process model (Figure 8) was designed to estimate survival, quality adjusted life years (QALYs) and costs over a 60 month time horizon following a given patient's and/or transplant surgeon's decision to accept or decline a kidney within a KDPI range of 51-60, 61-70, 71-80, 81-90 or 91-100. During simulation, the patient could be in one of four Markov states: transplanted with a kidney of patient-desired KDPI range (T); waiting list (W); failed transplant returning to waiting list to remain there until becoming deceased or receiving a second kidney transplant (F); deceased (D).

Figure 8. KDPI Offer Markov Decision Process Model



* T = transplanted with desired KDPI range; W = waiting list; F = failed transplant; D = death

Waiting list and transplant population survival was based on observational data from the Organ Procurement and Transplantation Network/Scientific Registry of Transplant Recipients (OPTN/SRTR) database from January 1, 2002 through December 31, 2011. Patients registered after January 1, 1997 but before January 2002 were counted as late entries and contributed person-time starting in January 2002. Analysis was restricted to adults (≥ 18 years old), those receiving kidney-only transplants, and complete cases. Graft survival by KDPI strata was calculated for all kidneys made available since 2002 with the median kidney used for calculations coming from the year 2011.

Follow up time and living status were based on the Social Security Death Master (SSDM) File and transplant center reports. Follow up time was counted as the longest follow up time as reported by the SSDM and transplant center.

Survival was modeled for waiting list and failure state patients using Cox proportional hazards models while competing risk Cox regression models were used for survival for those with a transplant (Table 14). The survival transition probability from the waiting list was stratified by whether the transplant candidate had a previous transplant in order to account for non-proportionality. All probabilities were parameterized by patient age, sex, weight, height, BMI, blood type, race/ethnicity, panel reactive antibody (PRA), primary diagnosis leading to kidney failure, history of previous transplant and time on dialysis. All models had their survival analyses run for KDPI ranges of 0-50, 51-60, 0-60, 61-70, 0-70, 71-80, 0-80, 81-90, 0-90, and 91-100. State transition models were validated, interactions were explored, and proportional hazards assumptions were verified using Martingale and Schoenfeld residuals. Time to transplantation from the waiting list with a kidney in the patient-desired KDPI range (W2T) was based on user input and for the purpose of this model, waiting time was drawn from a gamma distribution with the subsequent value being used as the mode.

Table 14 - State Transition Probabilities

Transition	Description	Source
W2T	Time to transplantation from waiting list with a patient-desired KDPI range donor kidney	User input; for model, mode taken from a gamma distribution
W2D	Time to death from waiting list; stratified by whether there was a previous transplant; Cox proportional model	SRTR data
T2F	Time to graft failure after transplant with a patient-desired KDPI range donor kidney; competing risk model	SRTR data
T2D	Time to death after transplant with a patient-desired KDPI range donor kidney; competing risk model	SRTR data
F2D	Time to death after graft failure in those patient who were either re-transplanted or remained on dialysis; Cox proportional model	SRTR data

QALYs were taken from a recent systematic review, meta-analysis and meta-regression of 190 studies evaluating patients undergoing various treatments for chronic kidney disease.[8] Transplantation had a mean utility of 0.82 (95% CI 0.74-0.90) and hemodialysis had a mean utility of 0.70 (95% CI 0.62-0.78). The W state used the same mean utility value as the hemodialysis and the D state had no QALYs associated with it.

Cost prediction models were built independently from the state transition probability models using the United States Renal Data System (USRDS) Medicare Payment Data for Parts A, B and D data from January 1, 2006 through December 31, 2010. All patients had at least one year of follow-up through December 31, 2011. Cost data was only collected for those who were using Medicare as their primary insurance during our enrollment period.

The cost prediction models predicted the cost per patient per month based on the state (T, W and F), specific T state costs where applicable (the T status was broken into three parts; first, the one time cost of the transplant associated admission, the monthly cost during the first year post transplant and the monthly cost for year 2-3 post transplant with this last number being used for years 4 and 5 as well), the individual patient characteristics (age, sex, race/ethnicity, primary diagnosis leading to renal failure, PRA, height, weight, BMI), and the KDPI strata (0-50, 51-60, 61-70, 71-80, 81-90, 91-100). Two additional models accounted for the cost of transplant admission and the cost after graft failure. Each model with its total number of observations and R-squared values are found below in Table 15**.**

Table 15 - Cost Prediction Models with Total Number of Observations and R-Squared Values

Cost model	Observations	R-squared values
T state (primary admission costs for transplantation operation)	25,852	0.0148-0.0419
T state (first year from transplantation)	29,565*	0.0310-0.0472
T state (years 2-3 from transplantation)	21,726	0.0299-0.0633
W state	67,267	0.0245
F state	3,016	0.0493-0.1491
Part D, T state (first year from transplantation)	21,773	0.0203-0.0600
Part D, T state (years 2-3 from transplantation)	16,956	0.0687-0.0939
Part D, W state	52,638	0.0217
Part D, F state	2,266	0.0359-0.1922

*Number of observations for T state (first year from transplantation) is larger than T state (primary admission costs for transplantation operation) as some individuals became eligible for Medicare after their transplantation.

In validating our costs, we compared them to published Medicare data.[9] The cost of dialysis via our model was $82,544 for one year compared to the USRDS Annual Data Report (ADR) 2013 Medicare value of about $75,000, our first year transplantation cost was $115,675 compared to the Medicare ADR value of $116,971 and our cost of transplantation per year for years 2 and 3 was $23,208 per year compared to the Medicare ADR value of about $20,000 all in 2011 U.S. dollars. All costs were reported in U.S. dollars discounted at 3% using 2011 as the base year.

Monte Carlo Simulation

Kaplan-Meier curves were generated from simulating each patient phenotype 1,000 times over a 60-month time horizon in 1-month intervals. The simulation was run for all the possible combinations of phenotypes (129,024) as well as each phenotype at five KDPI strata (51-60, 61-70, 71-80, 81-90 and 91-100) leading to 645,120 scenarios. Generated results included life-years gained, QALYs gained, and cost per QALY gained following a patient's decision to accept or reject a certain KDPI threshold.

Incremental survival, QALYs, costs and cost per QALYs

Ranges of minimum to maximum incremental survival, QALYs and costs at 5 years were calculated using a one percent sample of those who entered the waiting list between January 1, 2006 and December 31, 2010 (n=853). The percentage of those on the waiting list expected to benefit from increased survival, increased QALYs, decreased costs and negative cost per QALYs were then calculated from the same population.

Classification and Regression Tree Analysis (CART)

In order to determine the most important drivers of patient survival and QALYs, CART analysis was performed. The Markov model results of all 129,024 phenotypes were analyzed by CART as well as the Markov model results when stratified by KDPI range. The trees were pruned to a complexity parameter of 0.015 to minimize over-fitting.

Statistical Analysis

State transition probability analyses for survival were performed using STATA 12.0 (StataCorp LP, College Station, Texas). Cost modeling was performed using STATA MP 13.1 for Linux (StataCorp LP, College Station, Texas). The Markov model and Monte Carlo simulations were performed using C-plus-plus (Bjarne Stroustrup, Bell Labs). CART analysis was performed using R 2.14 (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Markov Model

The Markov decision process model was implemented allowing for 129,024 transplant candidate phenotypes based on the user input of age, sex, body mass index (BMI), blood type, race/ethnicity, panel reactive antibody (PRA), whether they had a previous transplant, primary diagnosis leading to renal failure and estimated months on the transplant waiting list. These phenotypes were then paired with one of five different KDPI strata (51-60, 61-70, 71-80, 81-90 and 91-100; based on donor age, height, weight, race/ethnicity, history of hypertension, history of diabetes, cause of death, serum creatinine, hepatitis C status and donation after circulatory death status) resulting in a total phenotype compliment of 645,120 scenarios. Once inputted into the model, survival curves were generated for a transplant candidate either accepting or rejecting an organ offer of specific KDPI range. The model also was able to determine quality-adjusted life years (QALYs) and cost-effectiveness over the same five year time period as the survival.

The following figures demonstrate survival curves for two different phenotypes (Figures 9-10).

Figure 9 - Expected Survival, Example 1. Expected survival after a deceased donor kidney offer at 5 years for a 40-year old female, BMI 25, blood type O, African American, PRA of 0, renal failure from diabetes, no prior transplant and with an estimated time on the waiting list of 24 months for either accepting or rejecting an organ with a KDPI of A) 51-60 or B) 91-100.

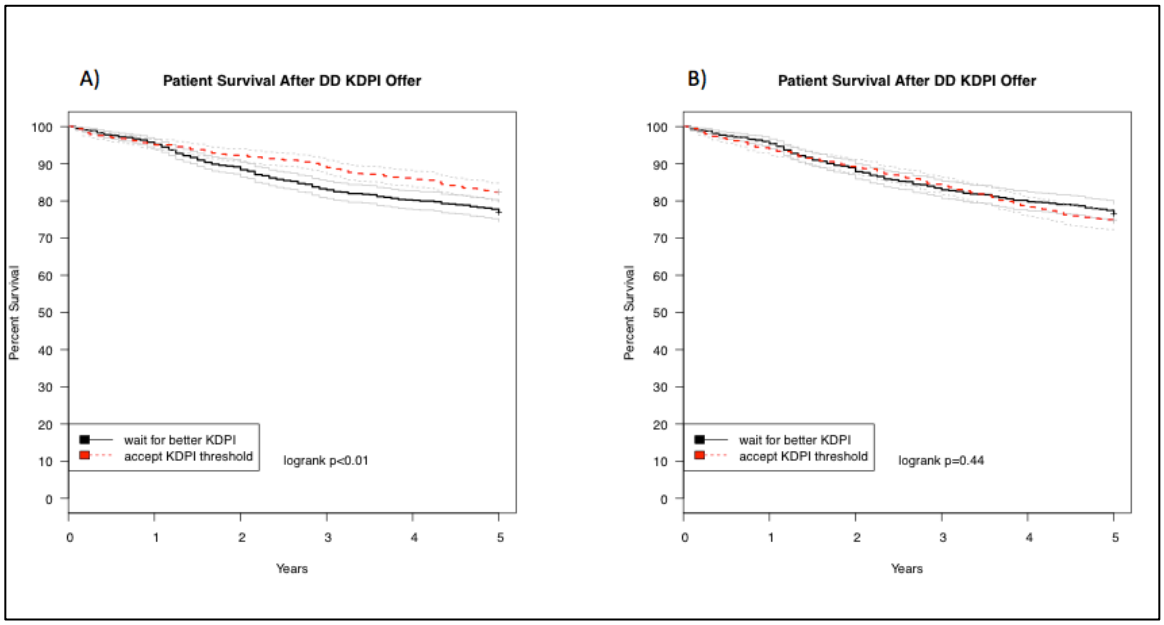
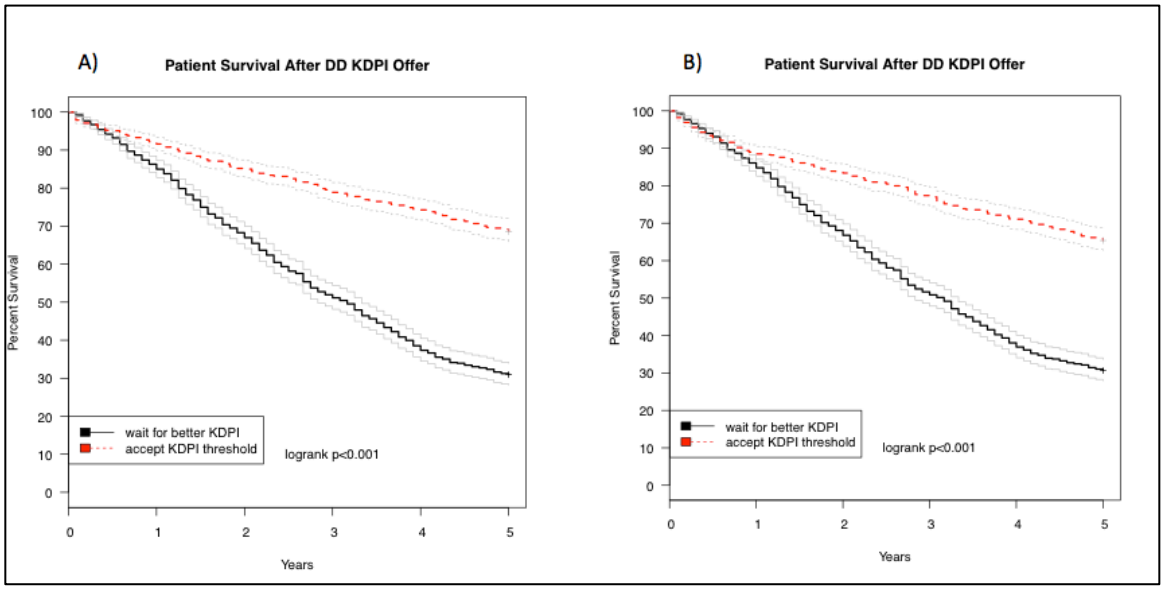


Figure 10 - Expected Survival, Example 2. Expected survival after a deceased donor kidney offer at 5 years for a 70-year old female, BMI 35, blood type A, Caucasian, PRA of 30, renal failure from glomerulonephritis, with a prior transplant and with an estimated time on the waiting list of 36 months for either accepting or rejecting an organ with a KDPI of A) 51-60 or B) 91-100.



In Example 1, there is a survival advantage by accepting an organ with a KDPI of less than 60 (graphs for KDPI 61-70, 71-80 and 81-90 not shown) while anything higher than a KDPI of 61 offers no distinct survival advantage and likely even worsens survival. In Example 2, there is a clear survival advantage in accepting any organ with any KDPI. From Table 16, it is also seen that there is a cost savings associated with accepting any organ with any KDPI through all four examples.

Table 16 - Increased Number of Lives and Cost Savings Associated with Accepting Any KDPI Threshold According to the Phenotypes Detailed in Figures 9-10

	Increase in those alive by accepting	Cost savings per person by accepting
Example 1		
KDPI 51-60	54	$134,35
KDPI 91-100	-16	$79,914
Example 2		
KDPI 51-60	376	$217,333
KDPI 91-100	347	$189,736

Survival, QALYs, Cost and Cost per QALY

Incremental survival, QALYs and costs were measured as additional percentage points of survival, additional QALYs, and additional cost, respectively, at 5-years for those accepting as opposed to rejecting a donated kidney of specified KDPI range for the 645,120 phenotypes stratified by KDPI range. Table 17 shows the incremental 5-year survival, QALY and cost associated with each KDPI strata and the percentage of phenotypes that would benefit from receiving a donated kidney from the specified KDPI strata as opposed to rejecting it. Cost per QALY was also calculated.

Table 17 - Incremental Survival, QALY, Cost and Cost per QALY by KDPI Range at 5 Years for All Generated Phenotypes. Results are displayed as "range; mean (percentage of those on the waiting list receiving the benefit of increased survival, increased QALYs, decreased costs, negative cost per QALY or negative cost per additional 1% increase in survival)."

	Incremental survival	Incremental QALY	Incremental cost	Cost per QALY	Cost per 1% increase in survival
KDPI 51-60	-29.9% - 64.2%; 5.1% (70.1%)	-0.7 – 2.2; 0.3 (89.9%)	-$265,901 - $120,258; -$65,451 (96.2%)	-$20,600,000 – $1,530,000; -$206,399 (87.5%)	-$2,383,691 - $2,391,834; -$6,629 (68.0%)
KDPI 61-70	-36.4% - 58.9%; 2.3%(54.2%)	-1.2 – 2.0; 0.3 (81.2%)	-$281,944 - $91,563; (96.3%)	-$2,560,000 - $2,120,000; -$184,794 (79.1%)	-$2,750,478 - $2,662,506; -$1,474 (53.2%)
KDPI 71-80	-48.0% - 68.2%; 2.4% (57.0%)	-1.7 – 2.4; 0.2 (77.2%)	-$199,536 - $296,949; -$49,887 (89.9%)	-$2,870,000 - $2,370,000; -$140,531 (74.3%)	-$1,591,965 - $1,722,243; -$1,427 (53.6%)
KDPI 81-90	-48.3% - 60.6%; 2.6% (58.2%)	-1.2 – 2.1; 0.2 (76.7%)	-$222,082 - $412,866; -$41,698 (84.9%)	-$2,200,000 – $2,880,000; -$124,159 (74.3%)	-$3,085,725 - $3,177,606; -$2,820 (57.9%)
KDPI 91-100	-51.9% - 61.4%; -1.1% (38.8%)	-1.2 – 2.1; 0.1 (59.0%)	-188,562 - $732,495; -$9,852 (69.7%)	-$5,410,000 - $4,330,000; -$117,147 (66.3)	-$2,578,700 - $4,086,837; -$1,618 (52.8%)

Graphs for the incremental cost per incremental survival and incremental cost per incremental QALY at 5 years for those accepting as opposed to rejecting a KDPI of a certain range are shown below (Figures 11-12). Of note, the same graphs stratified by only KDPI 91-100 are shown adjacent to the overall graph to show how the worst quality organs perform.

Figure 11 - Cost-Effectiveness in Incremental Cost to Incremental Survival Gain at 5 Years. The overall combination of all KDPI stratae are shown in A) and the KDPI strata of 91-100 is shown in B).

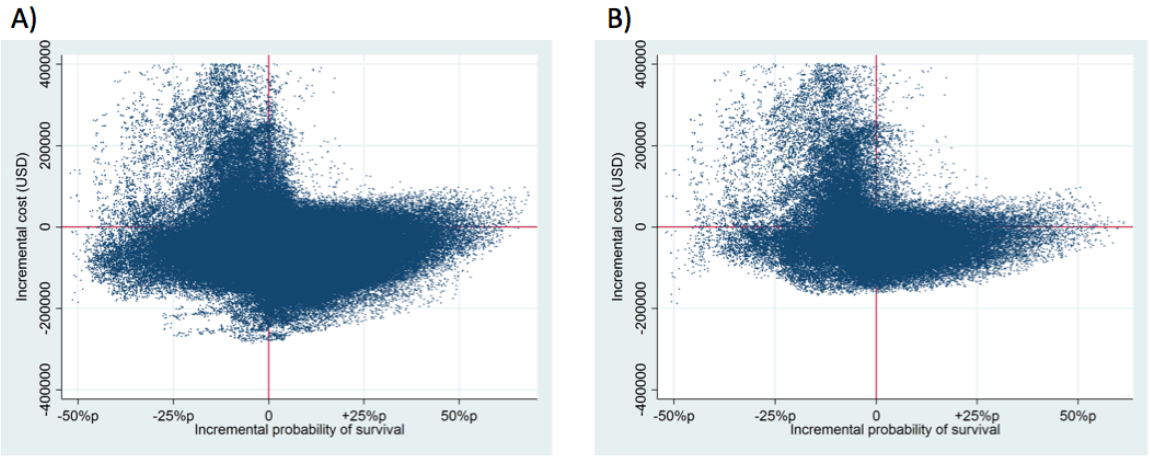
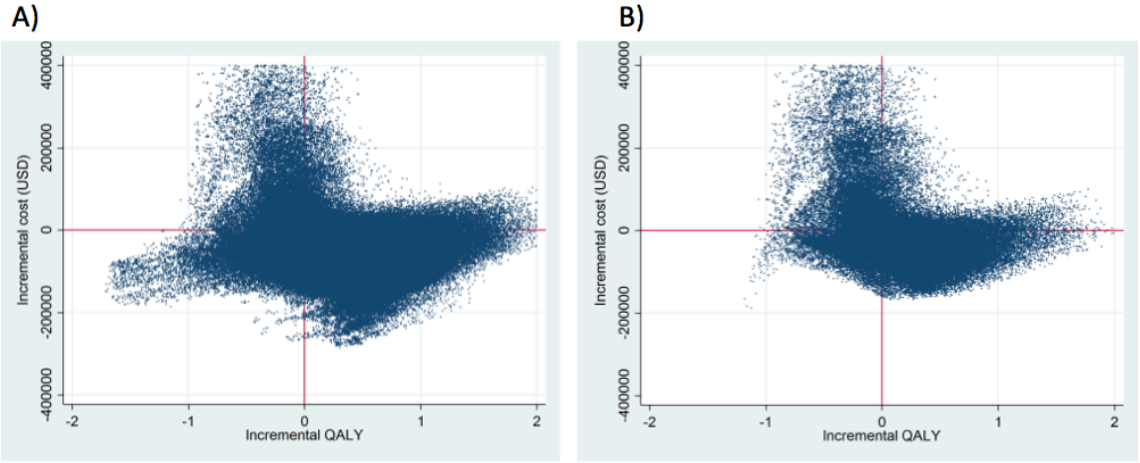


Figure 12 - Cost-Effectiveness in Incremental Cost to Incremental QALY Gain at 5 Years. The overall combination of all KDPI stratae are shown in A) and the KDPI strata of 91-100 is shown in B).



Survival, QALYs, Cost and Cost per QALY Applied to Waiting List

Incremental survival, QALYs and costs were measured as additional percentage points of survival, additional QALYs, and additional cost, respectively, at 5-years for those accepting as opposed to rejecting a donated kidney of specified KDPI range for a one-percent sample population of those who entered the waiting list from January 1, 2006 to December 31, 2010. Table 18 shows the incremental 5-year survival, QALY and cost associated with each KDPI strata and the percentage of waiting list candidates who would benefit from receiving a donated kidney from the specified KDPI strata. Cost per QALY was also calculated.

Table 18 - Incremental Survival, QALY, Cost and Cost per QALY by KDPI Range at 5 Years for All Those on the Waiting List. Results are displayed as "range; mean (percentage of those on the waiting list receiving the benefit of increased survival, increased QALYs, decreased costs or negative cost per QALY)."

	Incremental survival	Incremental QALY	Incremental cost	Cost per QALY
KDPI 51-60	-6.8 % - 40.2%; 11.1% (96.2%)	0.08 – 1.4; 0.58 (100%)	-$205,272 to -$33,991; -$119,968 (100%)	-$1,416,689 to -$27,635; -$234,082 (100%)
KDPI 61-70	-17.8% - 34.4%; 8.9% (90.7%)	-0.2 – 1.2; 0.5 (99.1%)	-$251,515 to -$48,953; -$122,161 (100%)	-$6,067,293 -$5,461,883; -$259,956 (99.1%)
KDPI 71-80	-26.3% - 33.2%; 8.4% (90.9%)	-0.5 – 1.2; 0.5 (99.4%)	-$176,519 -$112,255; -$108,508 (99.5%)	-$2,025,774 -$767,727; -$254,722 (99.2%)
KDPI 81-90	-27.6% - 32.8%; 5.8% (80.4%)	-0.3 – 1.2; 0.4 (97.9%)	-$161,770 -$196,913; -$98,710 (98.7%)	(97.7%)
KDPI 91-100	-43.2% - 31.9%; 4.7% (68.9%)	-0.7 – 1.2; 0.4 (95.8%)	-$143,513 -$240,909; -$70,985 (95.2%)	(93.3%)

CART: Most Important Factors in Survival

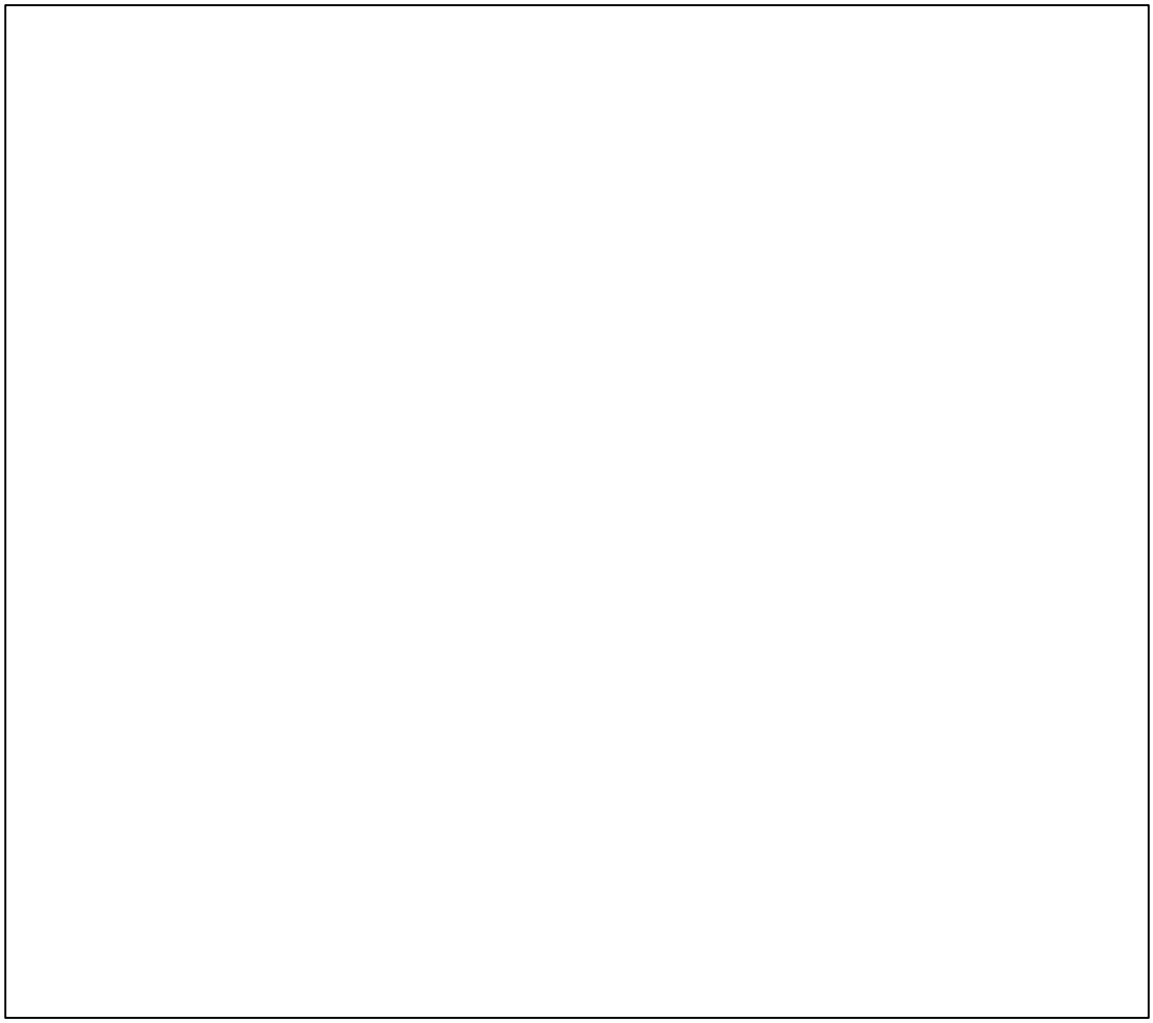
While all the transplant candidate factors affect 5-year survival, CART analysis identified the factors of most importance as estimated waiting time of 30 months, PRA of 90, age of 55 and prior transplant status. There was a 6.6% 5-year survival advantage for a transplant candidate to decline any organ with a KDPI of 50 or higher if they had an estimated time waiting time less than 30 months and a PRA over 90. There was a 24% 5-

year survival advantage in accepting any organ with a KDPI over 50 if their estimated waiting time was over 30 months, they had a PRA under 90, they were over 55 years old and were previously transplanted. Of note, KDPI was not identified as one of the most influential factors in 5-year survival by CART analysis.

CART: Most Important Factors in Survival Stratified by KDPI Range

The most important factors influencing 5-year survival stratified by KDPI included estimated waiting time of 15 or 30 months, PRA of 45 and 90, prior transplantation, race/ethnicity, age of 35, 45, 55, 65 and 75, blood type, and diagnosis leading to renal failure. The CART diagram for the KDPI stratification of 51-60 is shown in Figure 13. The CART diagram for the Survival Benefit of Accepting KDPI 50 shows an additional 5.1% survival at 5 years for accepting a kidney with KDPI of 51-60 after evaluating a total of over 129,000 phenotypes. Declining a kidney with a KDPI of 51-60 is a better option as there is a 2% added survival advantage at 5 years for those who have an estimated waiting time to transplantation of less than 30 months and who has a PRA over 90 (17% of the 129,000 phenotypes see this advantage). Accepting a kidney with a KDPI of 51-60 is a better option as there is a 20% added survival advantage at 5 years for those with an estimated waiting time to transplantation of over 30 months, a PRA less than 90 and are Caucasian (8% of the 129,000 phenotypes see this advantage) or for those with an estimated waiting time to transplantation of over 30 months, a PRA less than 90, are African American or Hispanic, with a prior transplantation and are over the age of 45 (5% of the 129,000 phenotypes see this advantage).

Figure 13. CART Analysis Demonstrating the Most Influential Drivers of Survival Stratified by KDPI Range

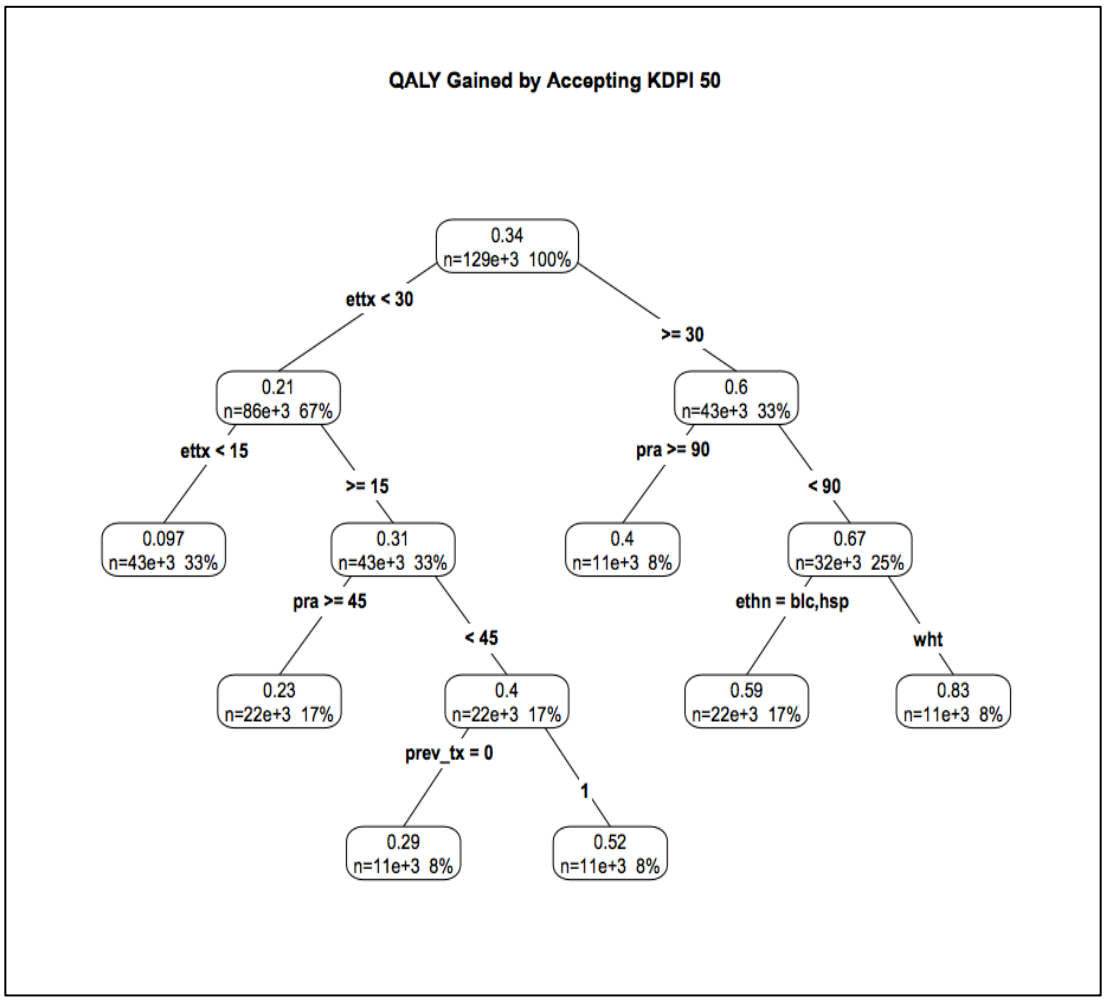


(*ettx = estimated months on waiting list, ethn blc = African American, ethn hsp = Hispanic, ethn wht = Caucasion, prev_tx=0 mean no prior transplant while prev_tx=1 mean prior transplant, abo = blood type specified as A, B, O and AB, dx = diagnosis as polycystic kidney disease (PKD), glomerulonephritis (GN) or diabetes (DM) or other.

CART: Most Important Factors in QALYs Stratified by KDPI Range

The most important factors influencing 5-year QALYs stratified by KDPI included estimated waiting time of 15, 21 and 30 months, PRA of 45 and 90, prior transplantation, race/ethnicity, age of 45, 55, and 65, blood type, and diagnosis leading to renal failure. The CART diagram for the KDPI stratification of 51-60 is shown in Figure 14. The CART diagram for the QALY Gained by Accepting KDPI 50 shows an added 0.34 QALYs at 5 years for accepting a kidney with KDPI of 51-60 after evaluating a total of over 129,000 phenotypes. There is no scenario associated with fewer QALYs so it is always advantageous to accept an organ of KDPI 51-60 in terms of QALY gains at 5 years. The most number of additional QALYs are experienced by those who accept a kidney with a KDPI of 51-60, have a waiting time to transplantation over 30 months, have a PRA less than 90 and are Caucasian as they experience an additional 0.83 QALYs at 5 years (8% of the 129,000 phenotypes see this advantage).

Figure 14 - CART Analysis Demonstrating the Most Influential Drivers of QALYs Stratified by KDPI Range



(*ettx = estimated months on waiting list, ethn blc = African American, ethn hsp = Hispanic, ethn wht = Caucasion, prev_tx=0 mean no prior transplant while prev_tx=1 mean prior transplant, abo = blood type specified as A, B, O and AB, dx = diagnosis as polycystic kidney disease (PKD), glomerulonephritis (GN) or diabetes (DM) or other

Discussion

Utilization of high KDPI kidneys (defined as any KDPI over 50) can offer survival and QALY advantage to a substantial group of transplant candidates at the same as providing a cost savings advantage to Medicare. Over 77% of the 129,024 phenotypes studied enjoyed cost savings to QALYs gained, 56% experienced a survival advantage and 87% realized an overall cost savings. Overall survival advantage was not driven by KDPI, but rather the most important factors in order of importance were waiting list time, PRA, age and prior transplantation. When stratified by KDPI range, the main drivers of survival and QALY were waiting list time, PRA, prior transplantation and race/ethnicity.

The growing disparity between the number of transplant candidates and available donor organs has lead to continued interest in how to increase and better utilize the scarce resource of donated kidneys. While some initiatives have sought to increase the donor supply (e.g. public awareness campaigns designed to encourage people to sign their drivers license as organ donors, encouraging living donation, evaluating theoretical markets for organs), others have sought to better utilize the organs that are already donated (e.g. establishing benefits of ECD or high KDPI kidneys, "longevity matching," and use of high infectious-risk organs). This paper focused on the more efficient utilization of donated kidneys by evaluating the utility and cost-effectiveness of using high KDPI kidneys as compared to the same individual remaining on the transplant waiting list even in the face of high KDPI kidneys conferring lower graft function as compared to lower KDPI kidneys.[10] Because while a lower quality organ confers lower

graft function and graft survival, their use can still provide overall survival, QALY and cost advantages to the transplant candidate compared to remaining on the waiting list.

Lower quality organs (as measured by ECD or KDPI) lead to lower graft function and survival due to higher rates of delayed graft function, more acute rejection episodes, decreased long term graft function, prolonged cold ischemia time, increased immunogenicity, impaired ability to repair tissue and impaired function.[11] So naturally, transplant surgeons and transplant candidates are more likely to turn down non-ideal organs. It is known that ECD and high KDPI kidneys are refused at a higher rate than SCD and lower KDPI kidneys.[6,11] Studies have shown that ECD organs confer survival benefit to at least some subgroups of transplant candidates over them remaining on the waiting list leading to a lower relative mortality resulting in 3-10 extra life years.[3,12] Similarly, a recent paper found that using high KDPI organs (71-80, 81-90, 91-100) in transplant candidates compared to remaining on the waiting list was associated with higher cumulative survival at 5 years in all three high KDPI groups.[7] Of note, while ECDS account for 15% of deceased donor organs, almost a third of ECDs have a KDPI of less than or equal to 85 and almost 5% of SCDs have a KDPI over 85.[2,5]

It now appears that the KDPI is gaining traction as the new standard for risk stratification of deceased donor kidneys. In March 2012, the Organ Procurement and Transplantation Network (OPTN) began including KDPI in DonorNet® at the time of organ offers to assist in assessing quality of deceased donor kidneys as well as to assist in "longevity matching."[2] Another utility of having a reliable and granular scoring system is that a

patient and provider should be able to prospectively discuss the risks and benefits of kidneys of different KDPI scores so that the candidate can determine the maximum degree of risk they are willing to accept according to KDPI score in terms of survival and QALYs.

There are several limitations to our paper. First, we used a model to simulate outcomes instead of reporting observed outcomes from a randomized control trail. We chose the modeling approach because it would not be possible to perform a prospective study where all 129,024 phenotypes of transplant candidates were assigned to accept or refuse a certain KDPI range and then to compare them to their counterfactual in any amount of reasonable time (not to mention cost nor ethical issues). While modeling may not reflect reality exactly, we feel that this model is a reasonable reflection as it was driven by data from a very large and comprehensive database, the Organ Procurement and Transplantation Network/Scientific Registry of Transplant Recipients (OPTN/SRTR) database. The model was tested for face validity and found to report survival, QALYs and costs reflecting the increase in survival and QALY and decrease in cost known when comparing transplantation to dialysis. Transition probability models were also tested for interactions and varying functional forms and competing risk models were used where appropriate.

Second, our costs were taken from the Medicare Payment Data of the United States Renal Data System and we only included those who had Medicare as their primary insurance provider. When calculating Medicare Part D costs, the population used was a subset of

those with Medicare as their primary insurance. While we only capture costs associated with Medicare recipients who use Medicare as their primary insurance, this represents a majority of those with end-stage renal disease. We felt that this was appropriate as we reported results in terms of cost to Medicare rather than cost to society.

Third, the R-values of our cost model were low meaning that they did not account for most of the variability in costs. However, the models did account for a number of patient and donated organ characteristics which made for a much better estimate of cost rather than just using the average cost across all patients.

Fourth, transplant recipients are only eligible for Medicare until their third anniversary from their transplant date. Our model used a 5-year time horizon so we used the Medicare year 2 and 3 costs per patient for years 4 and 5 as well. This seems to be appropriate as the first transplant year costs are significantly higher than the other years, but then the costs over the next two years are relatively stable so that Medicare reports those costs as the same for years 2 and 3. Since costs immediately stabilize in years 2 and 3, we felt that using the same stable costs for years 4 and 5 was acceptable.

Fifth, while use of high KDPI kidneys confer 5-year survival and QALY advantage, it is recognized that this is at the expense of increased short-term mortality.[7] So the results of this model should be interpreted with care by individual patients and physicians in light of this fact.

The findings of this study demonstrate that there is a wide range of high KDPI organs that can provide increased survival and QALYs even with decreased costs for a large group of subpopulations on the waiting list. The increased use of appropriate high KDPI kidneys in transplant candidates can represent a more efficient use of the donated organ pool and result in better candidate utility and cost savings to Medicare.

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CHAPTER FIVE – DISCUSSION ON METHODS

Literature Review Methods

Literature review many times is the first step in identifying or evaluating a topic of interest. When performing or communicating the results of such a search, it is helpful to follow a guideline-driven evaluation process. A well-used process to evaluate a specific topic by collating the evidence over a broad range of literature is the systematic review. However, another reason to review the literature might be to evaluate the breadth of research on a topic, determine if a full systematic review should be pursued, summarize research findings or identify gaps in the literature,[1] and in this case, a scoping review would be favored.

Scoping reviews were first formally advanced in 2005 by Arksey and O'Malley.[1] In their 2005 paper, they established guidelines for this type of review to make a uniform approach of the many different types of literature reviews that were being conducted under the headings of systematic review, meta-analysis, rapid review, literature review, narrative review, research synthesis and structured review. They put forth five stages to be included in a scoping review that included identifying the research question, identifying relevant studies, study selection, charting the data, and collating/summarizing then reporting the results. In terms of collating data, they used nine headings (interventions, sample sizes, participants, research methods, outcomes, evidence relating to effectiveness, economic aspects, UK studies and gaps in the research). Identification of

research gaps was centered around the literature review by comparing topics across interventions and study designs as well as the optional stage of expert consensus.

A subsequent paper in 2010 by Levac et al. sought to advance the methodology of scoping reviews in order to create consistency and to encourage others to participate in this type of review.[2] Their contributions, by "stage" as laid out by Arksey and O'Malley, were to clarify and link the research question with the purpose, recognizing balance of comprehensiveness with feasibility, using the iterative approach in study selection and data extraction, having a numeric summary and qualitative analysis of the results, considering the policy applications, and using stakeholder consultation in order to translate the research results.

As scoping reviews are still undergoing methodologic evolution, we turned to systematic review standards in order to carry out our scoping review. The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist and flow diagram were used for their intended consequences of creating transparency, standardization of steps and making reporting of results understandable and uniform across the literature. The checklist and worksheet can be found at www.prisma-statement.org.

The AHRQ guidelines for gaps analysis were made for systematic reviews,[3] but they were modified in our article to accommodate scoping reviews. The framework included identifying study characteristics such as population, intervention, comparison group, outcomes, and setting. Then a gap reason was assigned to that study from one of four

choices: insufficient or imprecise information, biased information, inconsistency or unknown consistency, and not the right information. Since systematic reviews focus on one question in a certain sub-population, the gaps analysis guidelines had to be widened in order to accommodate the breadth of scoping reviews (e.g. populations became adult versus pediatric for the scoping review instead of "gestational diabetes in women over the age of 40," for example, in a systematic review).

Economic Evaluation Methods

Economic evaluation is meant to help guide decision makers by relating the relationship between an intervention's cost and effect. While comparative-effectiveness research compares effectiveness outcomes, cost-effectiveness determines the cost associated with the effectiveness of the outcomes as well. There are several methods used in cost-effectiveness and include, to name a few, decision tree modeling, Markov modeling, difference-in-difference evaluation and instrumental variables approach. This thesis used a decision tree model as well as a Markov model in two separate cost-effectiveness analyses.

Cost-effectiveness can also serve to establish uniform practices in a health field marked by variation in treatments. The Dartmouth Institute for Health Policy and Clinical Practice, the New England Healthcare Institute, McKinsey consulting and Thomson Reuters have all estimated that 30% of the national spending in health care could be eliminated by reducing unwarranted variation in healthcare practices (lowering spending to the level of low spending regions while maintaining equivalent quality).[4] The

importance of this type of analysis is underscored by the existence of such groups and agencies that support this type of research like the Agency for Healthcare Research and Quality (AHRQ) on the U.S. federal level, the Institute for Clinical and Economic Review, and the New England Comparative Effectiveness Public Advisory Council as well as the fact that the 2009 U.S. government stimulus package included $1.1 billion for comparative effectiveness research.[5]

When choosing an economic analysis approach, there are a number of methods to choose from: cost analysis, cost-effectiveness, cost-utility and cost-benefit. Cost analysis evaluates cost with no measurement of outcomes. Cost-effectiveness evaluates both costs and outcomes with outcomes being measured per unit of specified result (e.g. outcome units of QALY, blood pressure points, years of survival). Cost-utility is a type of cost-effectiveness that evaluates both costs and outcomes with outcomes being measured as utilities (relative values of health states; most commonly used utility used is the quality adjusted life year or QALY). Cost-benefit analysis evaluates cost and outcomes with the outcomes converted to a monetary value.

Costs can include direct, indirect, and/or intangible costs. It is important to specify all costs that will be included and to assure that all costs that are incrementally different between the two interventions are included. Costs should all be discounted and reported in a uniform currency in a specific year. It is also important to specify the perspective of the analysis, meaning who is gaining the effect and who is paying for it. Common perspectives include that of the individual, the payer (in this thesis, that would be

Medicare) or society. The societal perspective includes not just costs of interventions and outcomes, but also the effect and costs of how that intervention fits in a societal context to include patient ability to be in the workforce, cost of informal caretakers for the patients, work absenteeism, and unintended consequences of the intervention, to name just a few.

Utility has been measured in the literature by QALY (one QALY equals living one year in perfect health), disability-adjusted life year (DALY; it is the years of life lived with a disability and the years of life lost with one DALY equivalent to one year of healthy life lost), healthy years equivalent (HYE; the amount of life in perfect health followed by immediate death that is equivalent to a lifetime in a diseased health state) and saved-young-life equivalent (the number of individuals deemed necessary with improved health to equal the saving of one young person's life).[6] There remains some controversy regarding the discounting of QALYs.[7]

QALY utility weights are evoked through time-trade-off, standard gamble and visual analogue scale. In all scenarios, individuals are asked their preference of living in certain health states or death as opposed to those health states. For time-trade-off, individuals are asked if they would prefer to remain in diseased health for a period of time, or to be restored to perfect health accompanied by a loss of years of life. Standard gamble asks the individuals if they would accept a treatment that could return them to perfect health or kill them as opposed to remaining in a diseased health state. The visual analogue scale merely asks individuals to rate a health state on a scale of 0 (death) to 100 (perfect health).

When performing a cost-effectiveness analysis, there is always the determination of whether the resultant cost-effective ratio is acceptable based on society's willingness to pay. Willingness to pay does not mean that interventions are sought that do not cost anything, but that interventions are paid for according to the value placed on them. Since many cost-effectiveness analyses are in cost per unit QALY, there should be a single value or range of costs that are willing to be paid for for any QALY. In the United Kingdom, the National Institute for Health and Clinical Excellence uses a general guideline of £20,000-30,000 (US$31,000-46,000) per QALY[8] as their threshold of cost-effectiveness. While there is an historical $50,000 per QALY cost-effective threshold used in the US literature,[9] the 2010 Patient Protection and Affordable Care Act specifically directs the newly formed Patient-Centered Outcomes Research Institute that no dollars per QALY threshold is to be used to determine recommendations for cost-effectiveness.[10] Another way to look at cost-effectiveness is to compare cost per QALY across other, common medical treatments or screenings. For example, colonoscopy screening every ten years for colorectal cancer (as compared to no screening) has a cost-effectiveness of $10,633-26,693 per QALY,[11] targeted digital mammography screening for breast cancer (as compared to all-film or all-digital screening strategies) has a cost-effectiveness of $21,000-33,000 per QALY,[12] and coronary artery bypass grafting has a life-time cost-effectiveness of $6,791 per QALY.[13]

As with most research methods, there are guidelines in how to conduct and report the outcomes of cost-effectiveness research in order to aid in the standardization of study

methods and to facilitate the ease of understanding reported results in the literature. One example is the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) that has developed such guidelines.[14]

When evaluating multiple variables, decision tree analysis and Markov modeling are two common methods to employ. Decision trees are helpful in structuring a course of events with multiple decision or outcomes branch points. Each branch is assigned a probability and the cohort then proceeds from the decision node down the branches to establish how many end up in each resultant state with the associated effectiveness and cost. However, decision tree models do not handle well explicit time lapse, continuing risk, competing risk over time, and alternate events over time.[15] In those cases, Markov modeling is helpful.

A Markov model consists of mutually exclusive health/disease states where individuals transition between states based on transition probabilities where the final state almost always is death. The individuals accumulate the attributes of the states they are in (e.g. cost, QALY, survival) based on the amount of time they spend in each state. In this manner, it is possible to predict outcomes for a cohort of patients over a defined period of time. One potential downside of Markov modeling is the "Markov assumption" where the model does not account for when or from what state the individual transitions once they transition to another state. This means that for any differential risk based on timing or prior state need to be built in by adding more states to the Markov model or that a form of dependency needs to be built into the transition probabilities.[15]

Transition probabilities determine how the cohort moves from one health state to another in Markov models and are survival models based on proportional or competing risks of the outcome of, basically, treatment failure or death. Model building is carried out in the standard fashion of data cleaning, population selection, parameter selection, regression evaluation for term interaction, confirmation of proportionality when using Cox proportional hazards and model validation.

Competing risk models are an alternative to Cox regression in survival analysis.[16] Competing risk regression accounts for outcomes other than the one of interest (e.g. recurrence after infectious disease treatment) in a fashion that is distinct from the censoring that occurs in Cox regression.[16] The key is that the risk group in the competing risk model is reduced with the occurrence of the competing risk or event whereas in the Cox regression the censored data is still considered to be at risk for the event of interest. When using Cox regression, the assumption of the censored individuals not contributing to the "at risk" group can be safely assumed if the only outcome of interest is death. Of note, in Cox regression, there is the also the assumption of proportionality where the hazard of the event of interest varies multiplicatively with a change in covariate (meaning the hazard ratio is constant over time). Since proportionality does not always hold, it needs to be explored and verified prior to finalization of the survival model.

Proportionality can be explored using graphical data where Kaplan-Meier observed survival curves are visually compared to Cox predicted survival curves for the same

covariate and if the curves are visually close to each other, then the assumption of proportionality is likely not violated. “Log –log” plots can also be used to assess the proportionality assumption where the log-log of survival versus the log of analysis time are plotted together and if the lines are reasonable parallel, then the assumption of proportionality is likely not violated.

Another test of proportionality is the Schoenfeld residuals test where independence is tested between scaled residuals and time where an outcome of a slope of zero confirms the proportionality assumption. Schoenfeld residuals are the difference between observed and expected values of failure for each individual for each covariate. As long as there is a random pattern in these residuals over time, then the assumption of proportionality has not been violated.

Martingale residuals are the difference between the observed and expected number of events for each individual and if these are summed over all individuals at a certain time, then one residual can be obtained for each failure time. Martingale residuals can be used to evaluate functional forms of covariates and well as to test the Cox proportionality assumption.[17] They usually are converted to deviance residuals so they are more symmetrically centered around zero and if they are plotted against the covariates, they should show a relatively random pattern around the mean of zero to show that the functional form or proportionality assumption is valid.

Lastly, results need to be evaluated for stability meaning covariates need to be evaluated over an appropriate range to see if their modification changes the overall outcome of the study. If the covariate has a determined range (e.g. sensitivity ranges from 95-98%), then deterministic sensitivity analyses can be employed where the sensitivity is varied in a step-wise fashion over its entire range. If the covariate and its range is better described by a probability distribution rather than specific values (e.g. probability of expiring at a certain time based on exposure and patient characteristics), then probabilistic sensitivity analyses can be employed. Regardless of type of sensitivity analysis used, it is important to evaluate results with some form of sensitivity analysis.

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CHAPTER SIX – HEALTH POLICY IN RENAL TRANSPLANTATION

The goal of many health-related studies is to improve the health of a population. The process through which that population health is improved is generally through health policy. The World Health Organization defines health policy as the pursuit of health care goals within the context of a future health vision through building consensus among stakeholders.[1]

While some scientific studies (e.g. comparisons of outcomes between different treatments) may not have policy implications as the health market will adjust according to price and outcome advantage through patient/provider preference and insurance coverage, there are some studies that need public policy to champion their cause in improving population health (e.g. smoking cessation campaigns). Public policy is brought about by government officials addressing public health problems that are felt to be unacceptable to the official or to the public in general.[2] Governmental intervention many times is in the form of distribution, redistribution or regulation in order to direct or influence the decisions, actions or behaviors of others in the face of market failures such as monopolies, negative or positive externalities, and information failures, to name a few instances. Public policies can originate in the legislative, executive, or judicial branches of government. When these public policies are centered around health, they are referred to as health policy. Health policy, by necessity due to the large field of health care, deals with topics including health care research, health systems, health care delivery, access to care, and quality of care to name just a very few.

The government works at several levels including national, state and local and functions through policies affecting guidance, operations or funding. In order to effectively promote change in the government through policy, policy must be made with these factors in mind recognizing that neglect of any one of the above-stated factors can lead to policy failure. National policies provide necessary guidance and leadership, operational policies are the means for implementing policies, and funding policies assure the financial viability of a policy.[3] It is also important to ensure the ability to "scale-up" a policy intervention. Scaling up is a deliberate effort to move from pilot testing an idea on a defined population to the general population at a reasonable rate and then to assure longevity of that intervention.[4]

Evidence-based policy has as a goal the adopting of public policy based on scientifically established objective data. This concept is the same as that of evidence-based medicine where the delivery of medical care is based on practices established by scientific studies. Of course, some issues are not well described by universally accepted quantitative methods and instruments so there still remains some room for differing opinions in evidence-based policy.

Kidney Transplantation

There a number of government and non-government agencies that play key roles in the care of end-stage renal patients. These include: Congress, which has been involved in

kidney transplantation for decades (Social Security Act, 1972; NOTA, 1984), the U.S. Department of Health and Human Services (HHS)[5] that awarded the first contract to UNOS to operate the OPTN, the United Network for Organ Sharing (UNOS), a private, non-profit organization tasked with operating the Organ Procurement and Transplantation Network, managing the wait list, arranging recipient and donor matches and maintaining a database, and the Organ Procurement Organizations (OPO's), which are non-profit organizations that evaluate and procure organs from deceased donors.

The work in this thesis lends itself to affecting change that would be made at the national level. First, the scoping review may provide evidence as to where that research might be best carried out by virtue of the gaps analysis although there was no formal comparative- or cost-effectiveness evaluation in the scoping review of the impact of the research in the different areas. However, the methodology of assessing the scope of the literature to determine research gaps may lead to operational policy change in funding mechanisms at the national level where grant funds would only be dispersed after a researcher conducted or reported a formal gaps analysis. The purpose of this would be to assure that research is being more efficiently carried out in areas of need rather than performing duplicated research in areas already saturated with studies.

Second, the cost-effectiveness paper on screening lends itself to national policy change at the OPTN level. In seeking to optimize outcomes (e.g. balancing utilizing the most non-infected organs and avoiding use of infected organs) at the lowest cost, the OPTN may decide to change national high-risk donor organ screening practices. The results of this

paper would have to be corroborated by further research and then it would be up to the working council of the OPTN to change the national screening policy or not.

Third, the Markov model paper also has the potential to affect policy at the OPTN level. While it has been known that marginal kidneys have benefit to those on the waiting list, it has not been elucidated by KDPI and patient phenotypes. The OPTN may form waiting lists by KDPI level so that individuals consent to receive certain KDPI level kidneys as they do now for high-infectious risk organs. In this manner, the discussion of risk and benefits of certain organs for an individual patient can be had prior to transplantation offer and potentially decrease the last-minute discussions of the risks of high KDPI organs, decrease the turn down of KDPI organs and subsequently decrease the increased cold ischemic time associated with organ turn down.

While the results of this thesis lend themselves to national guideline changes, it is still important that all of these different organizations involved in kidney transplantation be accounted for in order for the policy to be effective. It is recognized that establishing consensus among so many organizations and the government can be monumental as described by one participant in the passage of the Norwood Act of 2007 who said that "(t)hose involved in (that) process can attest that the passage of the Norwood Act was a herculean endeavor – for a modality that had no opposition from anyone in the medical community, the general public, or Congress."[6] There are an abundance of stakeholder organizations that can be called upon for support in policy efforts in the kidney transplantation community. A few of these organizations include the National Kidney

Foundation, the American Society of Transplant Surgeons, the American Society of Transplantation, the Association of Organ Procurement Organizations and the Transplant Recipients International Organization.

Important legislative work has been done recently by Johns Hopkins researchers and clinicians in the field of kidney transplantation. First, the Charlie W. Norwood Living Organ Donation Act of 2007[7] amends NOTA (1984) in specifically stating that human organ paired donation does not violate NOTA's prohibition of any human organ transfer for human transplantation for "valuable consideration." The policy change was prompted by Johns Hopkins researcher clinician, Dr. Dorry Segev, who published research across years and journals with multiple collaborators that showed the benefit of increased kidney transplants each year.[8,9] In addition, the Congressional Budget Office found that the legislation would save Medicare $500M over 10 years and the U.S. Justice Department issued a legal opinion at the request of the U.S. HSS stating that paired donations did not qualify as "valuable consideration."[10]

Second, the conception and passing of the HIV Organ Policy Equity (HOPE) Act of 2013[11] was also instigated by the research of Dr. Dorry Segev. The policy specifically amended the Public Health Service Act to repeal the OPTN directive that HIV positive organs from deceased donors could not be acquired or used in transplantation.[11] This policy was based on research in the potential pool of HIV-infected deceased donors that was estimated to be approximately 500-600 donors per year. It was argued that the use of those organs would significantly decrease the wait time for those with and without HIV

on the kidney transplant waitlist and thereby significantly decrease the associated mortality, morbidity and cost of kidney transplant candidates remaining on the waitlist.[12]

In summary, the three papers in this thesis serve to elucidate the more efficient use of research and utilization of marginal organ donations. The results of each paper have potential policy implication that would serve to improve research efforts and increase the survival and QALYs while potentially simultaneously decreasing the cost of care of those on the kidney transplant waiting list.

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APPENDIX - Curriculum Vitae

Trevor Ashton Ellison

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Education

2009 - Present	**Johns Hopkins School of Public Health, Baltimore, MD, USA**
	PhD Candidate in Economics and Health Policy
2010 - 2011	**Judge Business School, University of Cambridge, UK**
	Masters in Business Administration (MBA) – Gates-Cambridge Scholarship
2001 - 2005	**Johns Hopkins School of Medicine, Baltimore, MD, USA**
	MD degree – Student Society, Curriculum Reform Committee
1994 – 1995/	**Brigham Young University (BYU), Provo, UT, USA**
1997 - 2001	BS Zoology with Human Biology Emphasis – Cum Laude, University Honors
	Thesis, *Identifying Protein Binding Sites in the Enhancer Region of the Col11a2 Gene*

Work Experience

2005 – Present	**The Johns Hopkins Hospital, Baltimore, MD, USA**
	925-bed tertiary referral centre, ranked No.1 hospital in USA for 20 consecutive years
	General Surgery Resident, Department of Surgery

2010	**Fauna and Flora International, Cambridge, UK**
	World's first international conservation organization
	Consultant (as part of free, 5 week MBA project)
2010	**Cambridge Design Partnership, Cambridge, UK**
	Consulting company in the medical, consumer and cleantech sectors
	Consultant (as part of free, 5 week MBA project)
1999 – 2001	**Genetics Laboratory of Dr. Laura Bridgewater, Provo, UT, USA**
	Cancer Research Centre, Brigham Young University
	Bench researcher
1997 – 1998	**Missionary Training Centre, The Church of Jesus Christ of Latter-Day Saints, Provo, UT, USA**
	Church-sponsored training center for 3,800 missionaries
	Classroom and language instructor

Publications

Peer review articles

1. **Ellison TA,** Wolfgang CL, Shi C, Cameron JL, Murakami P, Mun LJ, Singhi AD, Cornish TC, Olino K, Meriden Z, Choti M, Diaz LA, Pawlik TM, Schulick RD, Hruban RH, Edil BH. A Single Institution's 26-Year Experience With Nonfunctional Pancreatic Neuroendocrine Tumors: A Validation of Current Staging Systems and a New Prognostic Nomogram. Annals of Surgery (2013)
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2. Le T., A. Shivaram, and J. Klein, eds. "Cardiovascular and Gastrointestinal topics," in First Aid Q & A for the USMLE STEP 2 CK. New York: McGraw-Hill, 2008.

Posters

1. Ellison, Trevor. *Pancreatic Neuroendocrine Tumors: A New Prognostic Tool*. Baltimore, MD, USA: Johns Hopkins Department of Surgery Research Poster Session, 2012.

2. Ellison, Trevor. *Tumor Size Correlates With Lymph Node Metastasis In Primary Pancreatic Endocrine Neoplasms*. Baltimore, MD, USA: Johns Hopkins Department of Surgery Research Poster Session, 2010 (1st prize).
3. Ellison, Trevor. *Tumor Size Correlates With Lymph Node Metastasis In Primary Pancreatic Endocrine Neoplasms*. New Orleans, LA, USA: Digestive Disease Week, 2010.
4. Ellison, Trevor. *The Role of Chemoradiation in the Management of Locally Advanced Pancreatic Endocrine Neoplasms*. New Orleans, LA, USA: 43rd Annual Meeting of The Pancreas Club, 2010.

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Presentations

1. Ellison, Trevor. *A Single Institution's 26-Year Experience with Non-Functional Pancreatic Neuroendocrine Tumors: A Validation of Current Staging Systems and a New Prognostic Nomogram.* The Gregory B. Bulkley Lecture in Surgical Research, Department of Surgery Research Day, Baltimore, MD, USA: Johns Hopkins, June 20, 2012.

Additional Information

Languages English (Native), Spanish (Fluent), Mandarin (Basic)

Achievements/Honors

2011 **Six Sigma**, Green Belt exam

2011	**Awarded competitive Loan Repayment Program** grant from the National Institutes of Health in the amount of $70,000 over two years
2009/11	**Awarded an NIH T32 grant** for studies in Economics and Health Policy
2009/11	**Niarchos Foundation Grant** recipient for studies in Economics and Health Policy
2003/5	**Elected as Medical Student Society representative**
Summer 1999	**Placed on Dean's Honor Roll**, Department of Biology and Agriculture, BYU
Summer 2000	**Awarded scholarship** for genetics research, Office of Research and Creative Activities, BYU
1994-1995	**Awarded Alvina S. Barrett Academic Scholarship,** full tuition
Summer 1999	**Volunteered in micro-credit lending** in Honduras, HELP International
1999-2001	**Co-director of Children with Disabilities,** BYU
1994	**Awarded the rank of Eagle Scout,** Boy Scouts of America
1994	**Early induction** into the National Cum Laude Society
1994	**Early acceptance** into the National Honor Society
1994	**Awarded AP Distinguished Scholar**, National Latin Test and National Spanish Test awards
Interests	Running; cycling; equestrian show jumping and polo; sailing; reading (politics, economics, medicine); travel; debating; learning the guitar

Helpful Links

JHH Resident Named Cambridge Gates Scholar BYU Grad Selected As Gates Scholar